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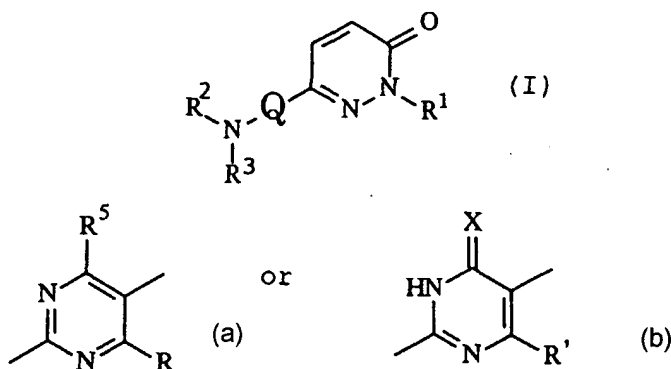
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(54) Title: AMINOPYRIMIDINE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM



(57) Abstract: An aminopyrimidine compound of the following formula (I), wherein Q is (a) or (b) in which R and R' are each optionally substituted aryl or heterocyclic group, R² is hydrogen, halogen, lower alkyl, optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfanyl or lower alkylsulfonyl, and X is oxygen or sulfur; R¹ is hydrogen, optionally substituted lower alkyl or cyclo (lower) alkyl which may be interrupted by an oxygen atom;

R² and R³ are each independently hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl, R² and R³ may be combined together with N atom to which they are attached to form N-containing heterocyclic group; or a salt thereof. The aminopyrimidine compound (I) and salt thereof of the present invention are adenosine antagonists and are useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure and the like.

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AMINOPYRIMIDINE COMPOUNDS, PROCESSES FOR THEIR PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

TECHNICAL FIELD

The present invention relates to a novel aminopyrimidine
5 compound and a salt thereof, which are useful as medicaments.

BACKGROUND ART

2-Amino-4-aryl-5-(6-oxo-1,6-dihydro-pyridazin-3-yl)-
pyrimidine compounds and derivatives thereof are novel, so
there has been no knowledge about these compounds. In addition,
10 any aminopyrimidine compounds having both of adenosine A₁ and
A_{2a} inhibitory activities are not known.

DISCLOSURE OF INVENTION

The present invention relates to a novel aminopyrimidine
compound and a pharmaceutically acceptable salt thereof, which
15 are useful as medicaments; processes for the preparation of
said aminopyrimidine compound and a salt thereof; a
pharmaceutical composition comprising, as an active ingredient,
said aminopyrimidine compound or a pharmaceutically acceptable
salt thereof; a use of said aminopyrimidine compound or a
20 pharmaceutically acceptable salt thereof as a medicament; and
a method for using said aminopyrimidine compound or a
pharmaceutically acceptable salt thereof for therapeutic
purposes, which comprises administering said aminopyrimidine
compound or a pharmaceutically acceptable salt thereof to a
25 human being or an animal.

The aminopyrimidine compound and a salt thereof are
adenosine antagonists (especially, A₁ receptor and A₂
(particularly A_{2a}) receptor dual antagonists) and possess various
pharmacological actions such as anticatalepsy action, cognitive
30 enhancing action, analgesic action, locomotor action,
antidepressant action, diuretic action, cardioprotective action,
cardiotonic action, vasodilating action (e.g. cerebral
vasodilating action, etc.), the action of increasing the renal

blood flow, renal protective action, improvement action of renal function, enhancing action of lipolysis, inhibition action of anaphylactic bronchoconstriction, acceleration action of the insulin release, the action of increasing the production of erythropoietin, inhibiting action of platelet aggregation, or the like.

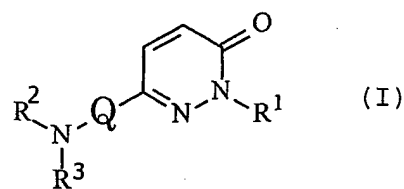
They are useful as cognitive enhancer, antianxiety drug, antidementia drug, psychostimulant, analgesic, cardioprotective agent, antidepressant, ameliorants of cerebral circulation, tranquilizer, drug for heart failure, cardiotonic agent, antihypertensive agent, drug for renal failure (renal insufficiency), drug for renal toxicity, renal protective agent, drug for improvement of renal function, diuretic, drug for edema, antiobesity, antiasthmatic, bronchodilator, drug for apnea, drug for gout, drug for hyperuricemia, drug for sudden infant death syndrome (SIDS), ameliorants of immunosuppressive action of adenosine, antidiabetic agent, drug for ulcer, drug for pancreatitis, drug for Meniere's syndrome, drug for anemia; drug for thrombosis, drug for myocardial infarction, drug for obstruction, drug for arteriosclerosis obliterans, drug for thrombophlebitis, drug for cerebral infarction, drug for transient ischemic attack, drug for angina pectoris, or the like;

and useful for the prevention and/or treatment of depression, dementia (e.g. Alzheimer's disease, cerebrovascular dementia, dementia accompanying Parkinson's disease, etc.), Parkinson's disease, anxiety, pain, cerebrovascular disease (e.g. stroke, etc.), heart failure; hypertension (e.g. essential hypertension, nephrogenous hypertension, etc.); circulatory insufficiency (acute circulatory insufficiency) caused by, for example, ischemia/reperfusion injury (e.g. myocardial ischemia/reperfusion injury, cerebral

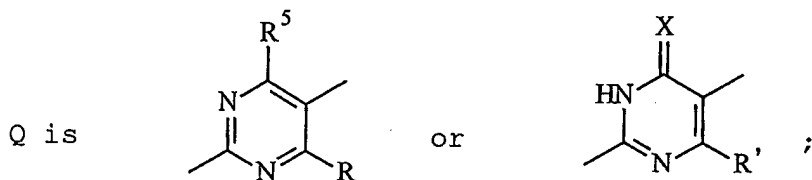
- ischemia/reperfusion injury, peripheral ischemia/reperfusion injury, etc.), shock (e.g. endotoxin shock, hemorrhagic shock, etc.), surgical procedure, or the like; post-resuscitation asystole;
- 5 bradyarrhythmia;
electro-mechanical dissociation;
hemodynamic collapse;
SIRS (systemic inflammatory response syndrome);
multiple organ failure;
- 10 renal failure (renal insufficiency) (e.g. acute renal failure, etc.), renal toxicity [e.g. renal toxicity induced by a drug such as cisplatins, gentamicin, FR-900506 (disclosed in EP-0184162), cyclosporin (e.g. cyclosporin A) or the like; glycerol, etc.], nephrosis, nephritis, edema (e.g. cardiac
- 15 edema, nephrotic edema, hepatic edema, idiopathic edema, drug edema, acute angioneurotic edema, hereditary angioneurotic edema, carcinomatous ascites, gestational edema, etc.);
obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer such as
- 20 peptic ulcer (e.g. gastric ulcer, duodenal ulcer, etc.),
pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus (e.g. mechanical ileus, adynamic ileus, etc.); and
myocardial infarction, thrombosis (e.g. arterial thrombosis,
- 25 cerebral thrombosis, etc.), obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack, angina pectoris, or the like.

The novel aminopyrimidine compound of the present invention can be shown by the following formula (I).

30



wherein



in which

R and R' are each optionally substituted aryl or heterocyclic group,

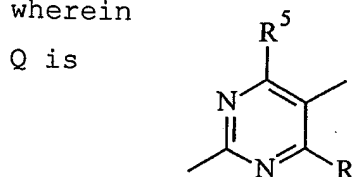
R⁵ is hydrogen, halogen, lower alkyl, optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfinyl or lower alkylsulfonyl, and

X is oxygen or sulfur;

R¹ is hydrogen, optionally substituted lower alkyl or cyclo(lower)alkyl which may be interrupted by an oxygen atom; R² and R³ are each independently hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl, R² and R³ may be combined together with N atom to which they are attached to form N-containing heterocyclic group; or a salt thereof.

The preferred embodiments of the aminopyrimidine compound of the present invention represented by the general formula (I) are as follows.

(1) The aminopyrimidine compound of the general formula (I) wherein



in which R and R⁵ are each as defined above,

R¹ is optionally substituted lower alkyl, and

R² and R³ are defined above.

(2) The aminopyrimidine compound of (1) above
wherein

R^1 is lower alkyl or lower alkoxy(lower)alkyl, and
 R^5 is hydrogen.

(3) The aminopyrimidine compound of (2) above
wherein

R^1 is lower alkyl, and
 R^2 is hydrogen.

(4) The aminopyrimidine compound of the general formula (I)
wherein

R^1 is hydrogen, lower alkyl, hydroxy(lower)alkyl, lower
alkoxy(lower)alkyl or phenyl(lower)alkyl,

R^2 is hydrogen, lower alkyl, lower alkanoyl or optionally
substituted benzoyl,

R^3 is hydrogen, lower alkyl, phenyl, pyridinyl(lower)alkyl or
-CO- R^{31} ,

in which R^{31} is lower alkyl, cyclo(lower)alkyl, lower
alkoxy(lower)alkyl, optionally substituted lower alkoxy,
optionally substituted phenyl or pyridinyl,

R^2 and R^3 may be combined together with N atom to which they
are attached to form N-containing heterocyclic group;

R and R' are each

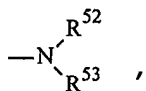


in which R^4 is hydrogen, halogen, hydroxy, lower alkyl,
optionally substituted lower alkoxy, trihalo(lower)alkyl,
lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl,
and n is an integer from 1 to 3,
provided R^4 may be different from each other when n is 2
or 3; and

R⁵ is hydrogen, halogen, lower alkyl, lower alkylthio, lower alkanoylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl,

-O-R⁵¹,

- 5 in which R⁵¹ is hydrogen, optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or



- 10 in which R⁵² is hydrogen or lower alkyl;
R⁵³ is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group,
R⁵² and R⁵³ may be combined together with N atom to which
15 they are attached to form N-containing heterocyclic group; or a salt thereof.

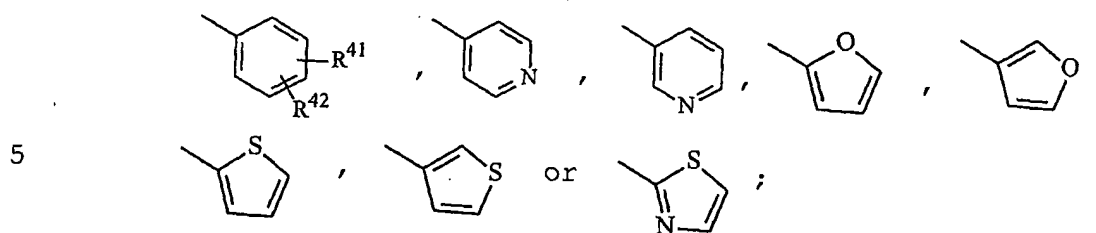
(5) The aminopyrimidine compound of (4) above wherein

- 20 R¹ is hydrogen, methyl, ethyl, propyl, isopropyl, hydroxyisopropyl, methoxyisopropyl or benzyl;
R² is hydrogen, methyl, acetyl, benzoyl, toluoyl, methoxybenzoyl, trifluoromethylbenzoyl, fluorobenzoyl or chlorobenzoyl;
R³ is hydrogen, methyl, phenyl, pyridinylmethyl or
25 -CO-R³¹,

- in which R³¹ is methyl, propyl, isopropyl, isobutyl, tert-butyl, cyclopropyl, cyclohexyl, methoxy, methoxymethyl, trichloroethoxy, phenyl, tolyl, methoxyphenyl, trifluoromethylphenyl, fluorophenyl,
30 chlorophenyl or pyridinyl, and

R² and R³ may be combined together with N atom to which they are attached to form morpholino;

R and R' are each

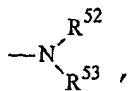


10 in which R⁴¹ and R⁴² are each independently hydrogen, fluoro, bromo, chloro, hydroxy, methyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, isopentyloxy, hexyloxy, methoxyethoxy, fluoroethoxy, fluoropropoxy, dimethylaminoethoxy, morpholinylethoxy, methylthio, methylsulfinyl or methylsulfonyl; and

15 R⁵ is hydrogen, fluoro, methyl, methylthio, acetylthio, phenylthio, methylsulfinyl, methylsulfonyl, -O-R⁵¹,

20 in which R⁵¹ is hydrogen, methyl, ethyl, propyl, isopropyl, allyl, propynyl, cyclobutyl, cyclohexyl, hydroxyethyl, methoxyethyl, carboxymethyl, aminoethyl, dimethylaminoethyl, fluoroethyl, carbamoylmethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, cyclopropylcarbamoylmethyl, methoxycarbonylmethyl, tert-butoxycarbonylmethyl, acetylmethyl, benzoylmethyl, phenyl, benzyl, pyridinylmethyl, pyridinylethyl, tetrahydro-2H-pyranyl or 1,3(2H)-dioxoisindolinylethyl,

25 or



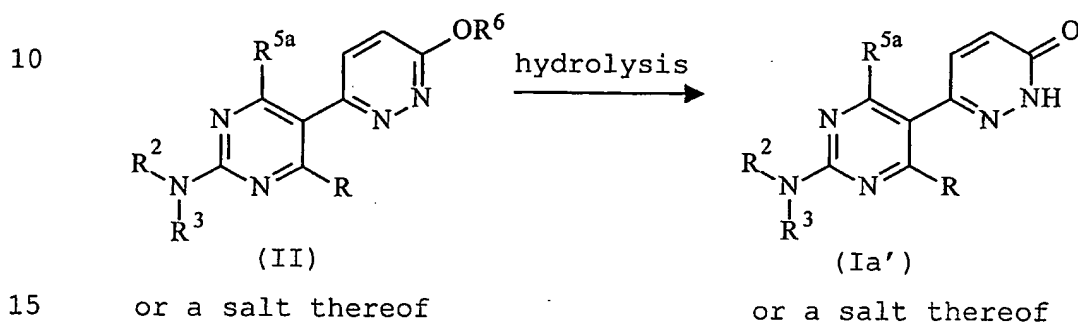
in which R⁵² is hydrogen or methyl, R⁵³ is hydrogen, methyl, ethyl, propyl, isopropyl, tert-butyl, allyl, cyclopropyl, hydroxyethyl, methoxyethyl, aminoethyl, dimethylaminoethyl, carbamoylmethyl, amidino, phenyl, benzyl, pyridinyl, pyridinylmethyl, furylmethyl or dimethylthiazolyl,

R^{52} and R^{53} may be combined together with N atom to which they are attached to form pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl or benzimidazolyl,

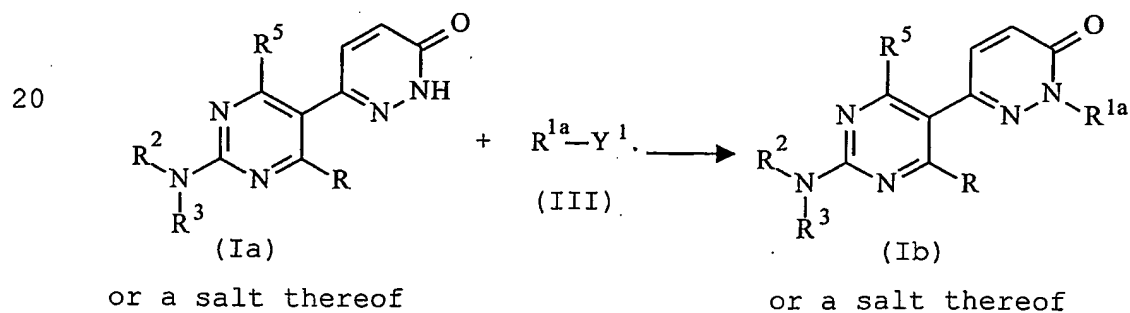
5 or a salt thereof.

The object compound (I) and a salt thereof of the present invention can be prepared by the following processes.

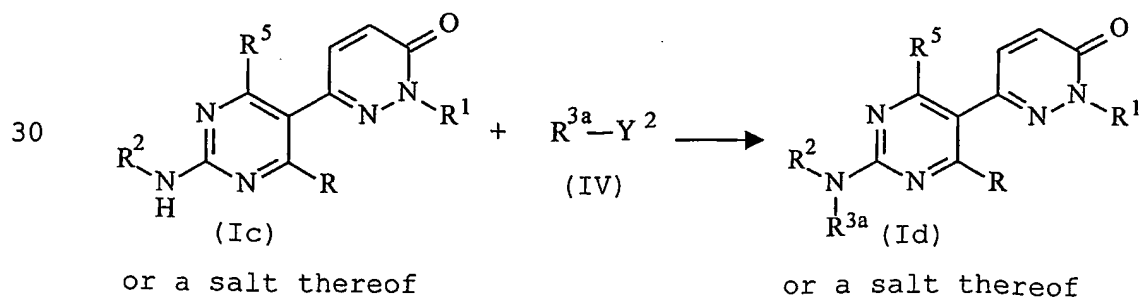
Process 1

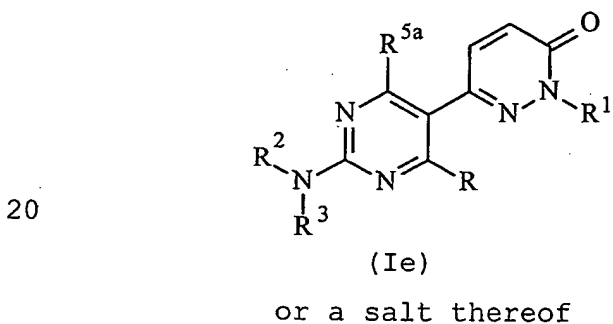
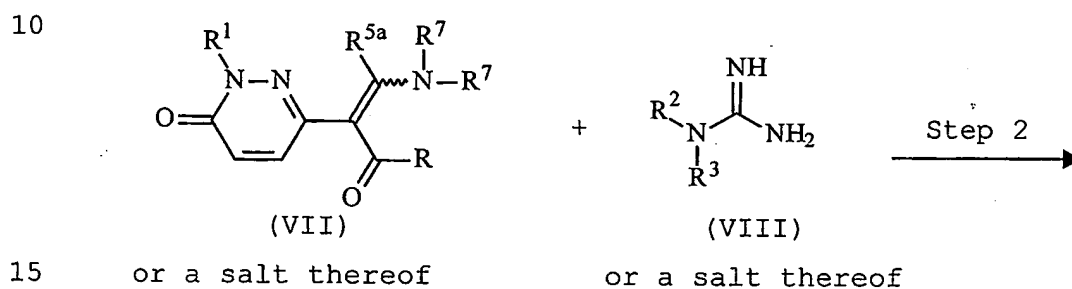
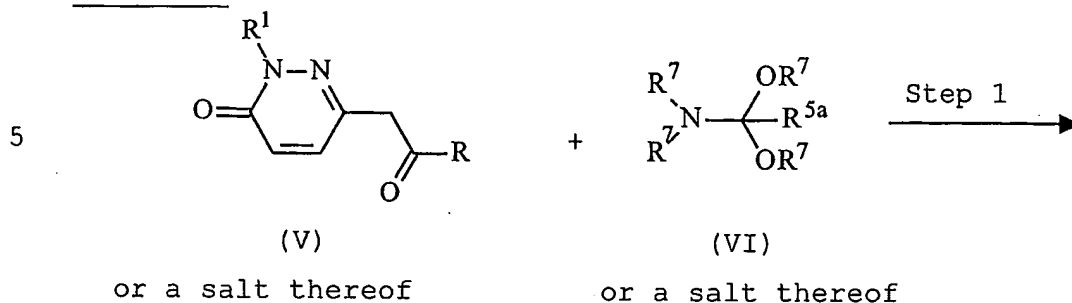
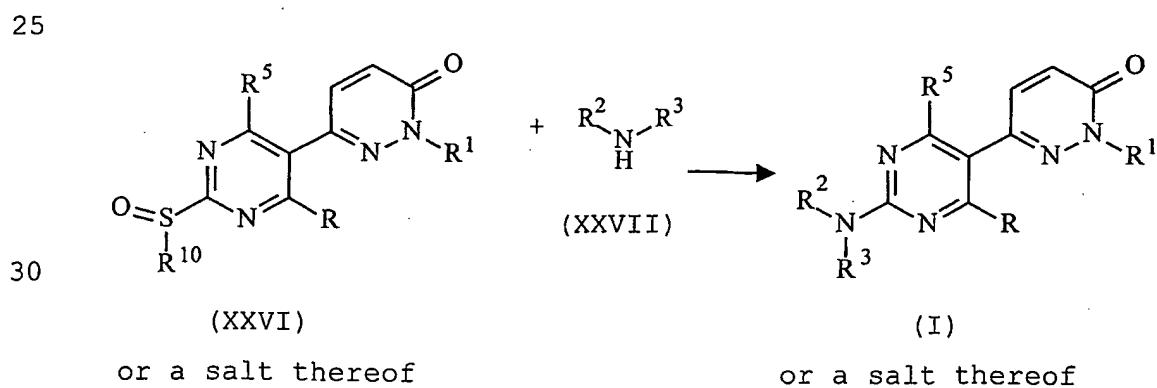


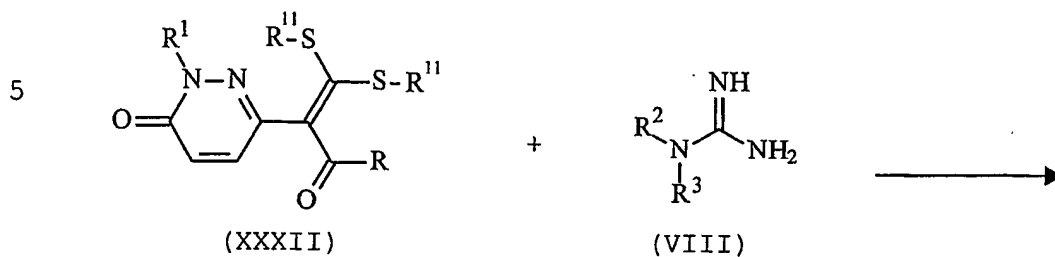
Process 2



Process 3



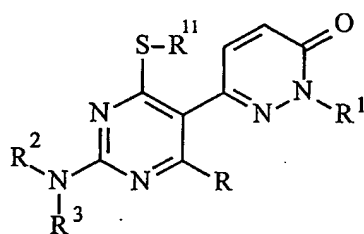
Process 4Process 5

Process 6

or a salt thereof

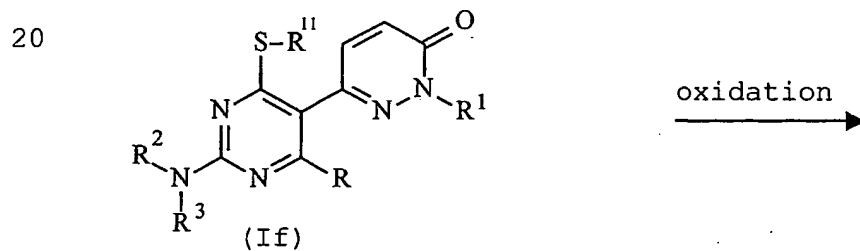
or a salt thereof

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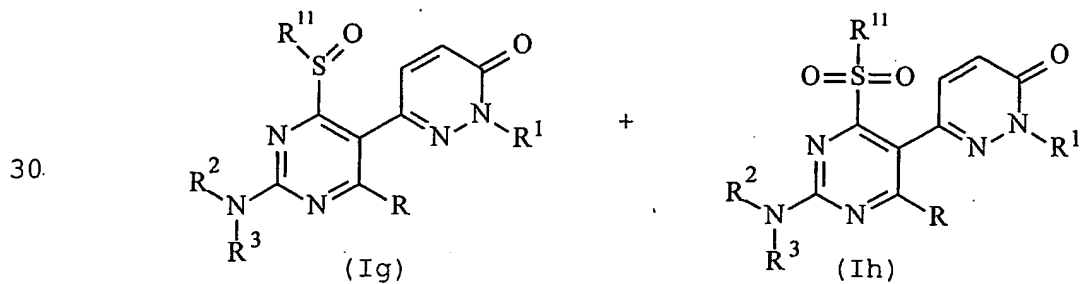
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or a salt thereof

Process 7

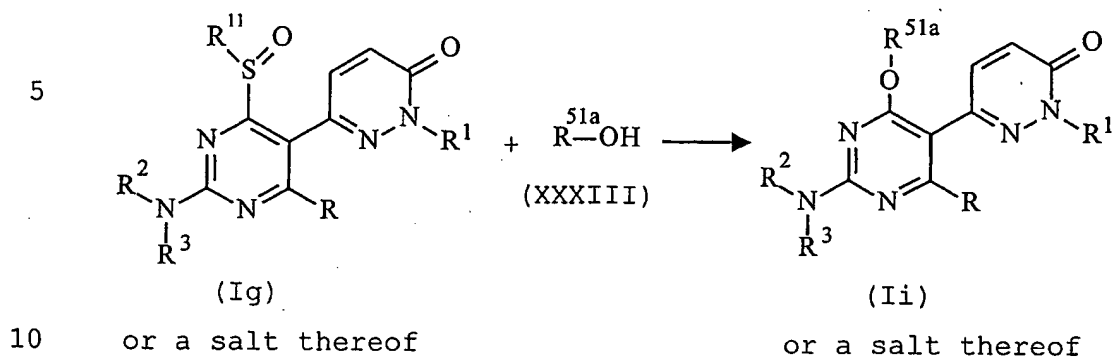
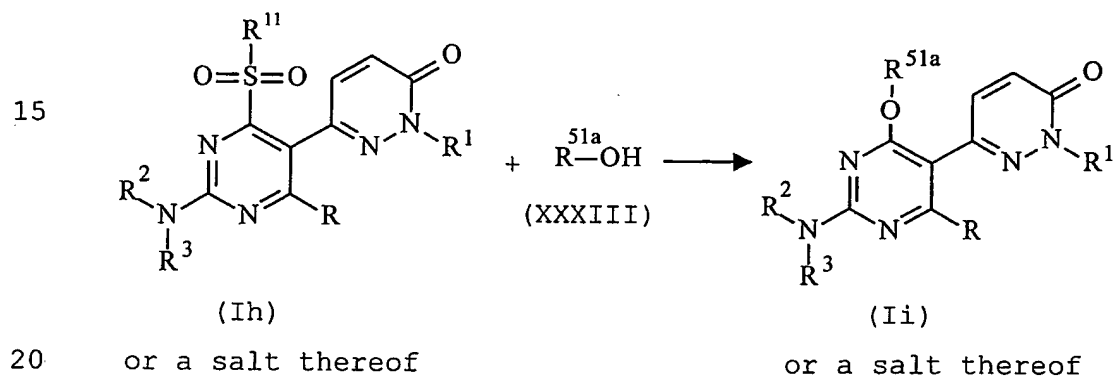
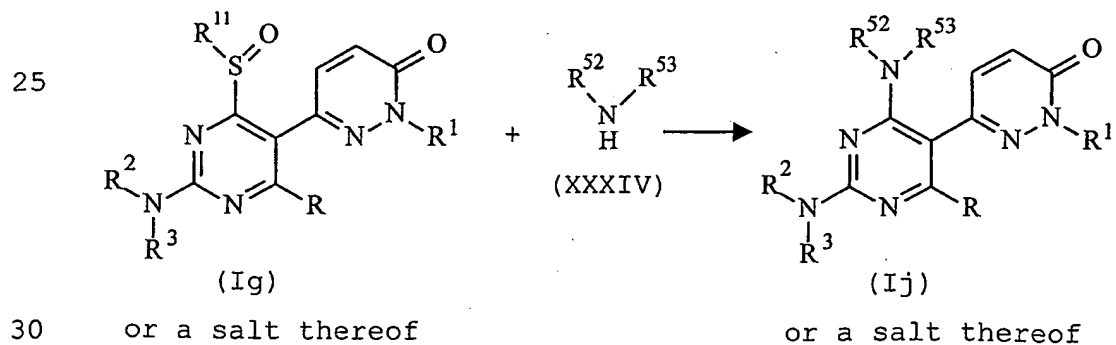
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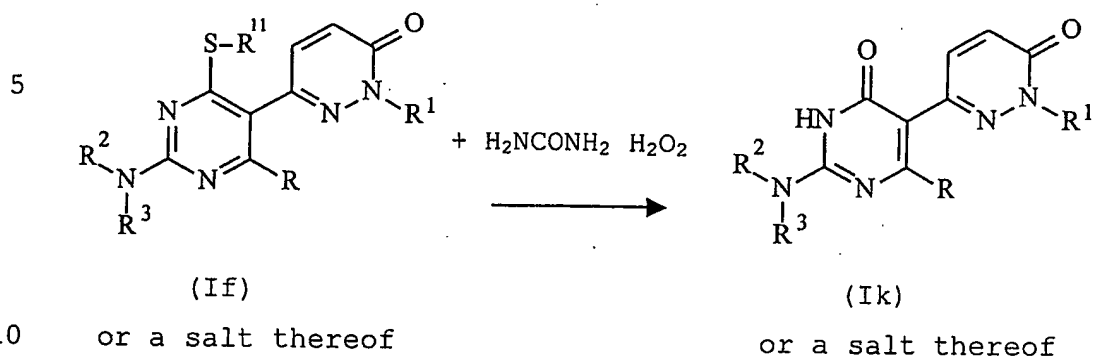
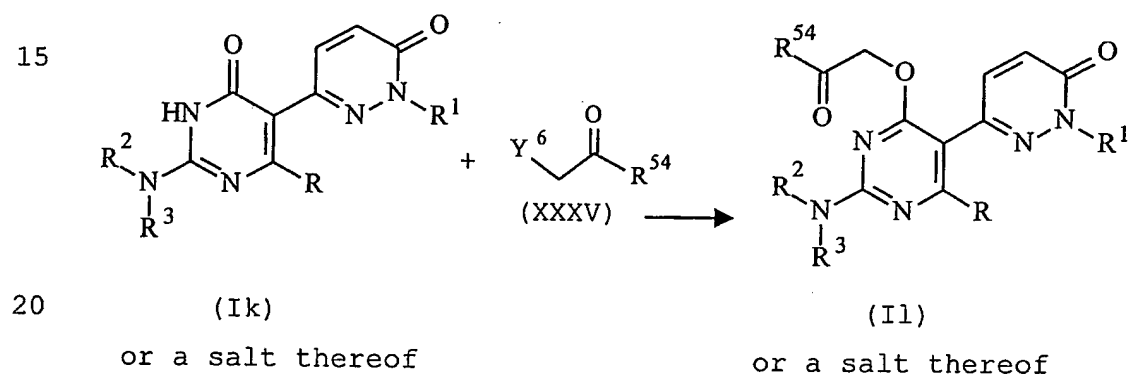
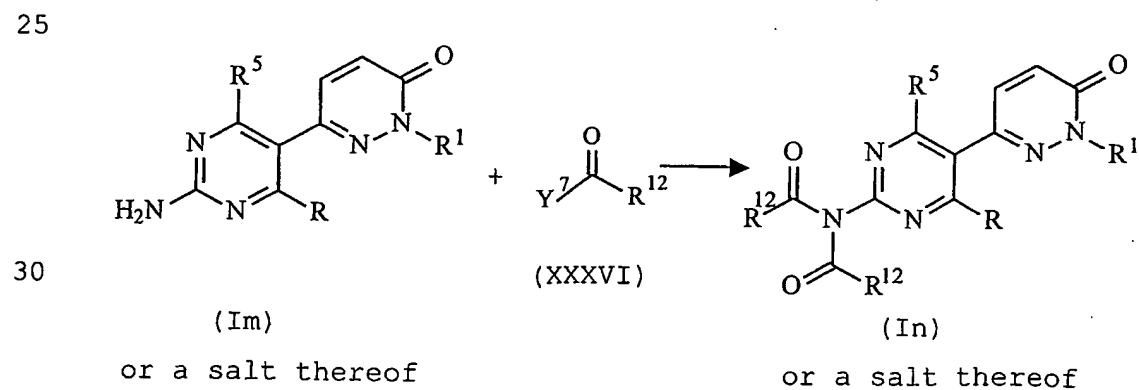
or a salt thereof

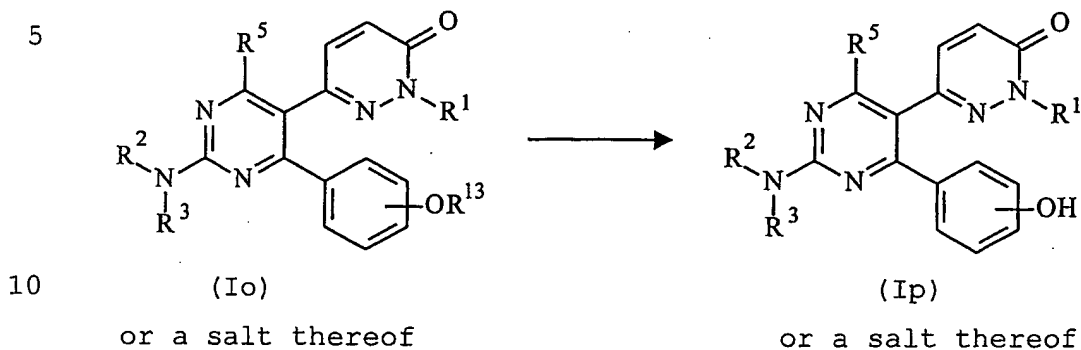
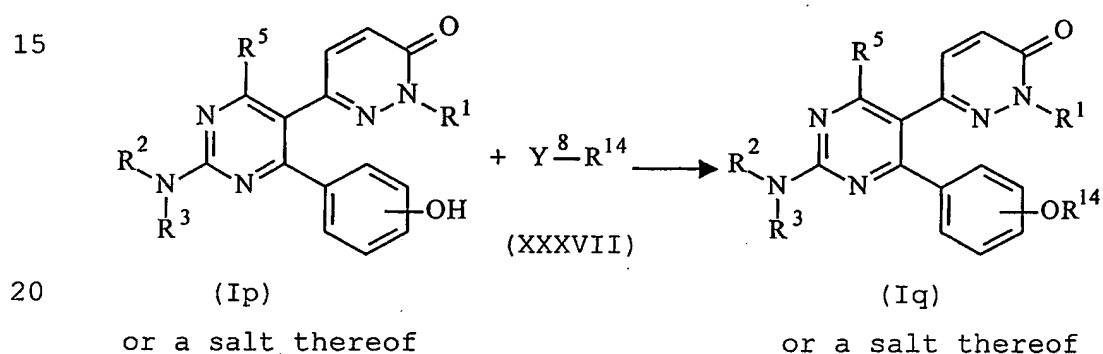
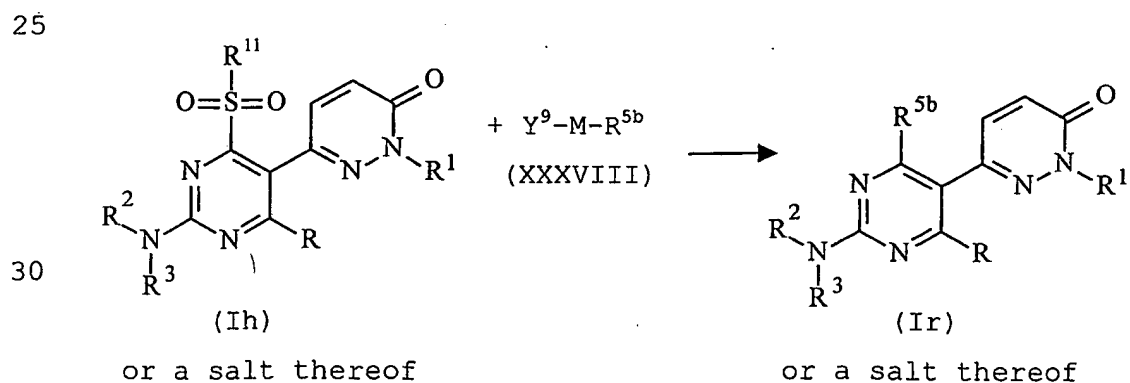


or a salt thereof

or a salt thereof

Process 8Process 9Process 10

Process 11Process 12Process 13

Process 14Process 15Process 16

wherein

R is optionally substituted aryl or heterocyclic group;

R¹ is hydrogen, optionally substituted lower alkyl,
cyclo(lower)alkyl which may be interrupted by an oxygen atom
or aryl(lower)alkyl;

R^{1a} is optionally substituted lower alkyl, cyclo(lower)alkyl
which may be interrupted by an oxygen atom or aryl(lower)alkyl;

R² and R³ are each independently

hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl,

R² and R³ may be combined together with N atom to which they
are attached to form N-containing heterocyclic group;

R^{3a} is lower alkyl, acyl, aryl or heterocyclic(lower)alkyl;

R⁵ is hydrogen, halogen, lower alkyl, optionally substituted
hydroxy, optionally substituted amino which may form

N-containing heterocyclic group, optionally substituted
mercapto, lower alkylsulfinyl or lower alkylsulfonyl;

R^{5a} is hydrogen, lower alkyl, optionally substituted hydroxy
or optionally substituted amino;

R^{5b} is lower alkyl;

R^{51a} is optionally substituted lower alkyl, lower alkenyl, lower
alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group,

R⁵² is hydrogen or lower alkyl;

R⁵³ is hydrogen, optionally substituted lower alkyl, lower alkenyl,
cyclo(lower)alkyl, amidino, aryl or heterocyclic group,

R⁵² and R⁵³ may be combined together with N atom to which they
are attached to form N-containing heterocyclic group;

R⁵⁴ is lower alkyl, cyclo(lower)alkyl, lower alkoxy or aryl;

R⁶, R⁷, R¹⁰, R¹¹ and R¹³ are each lower alkyl;

R¹² is optionally substituted aryl or lower alkoxy;

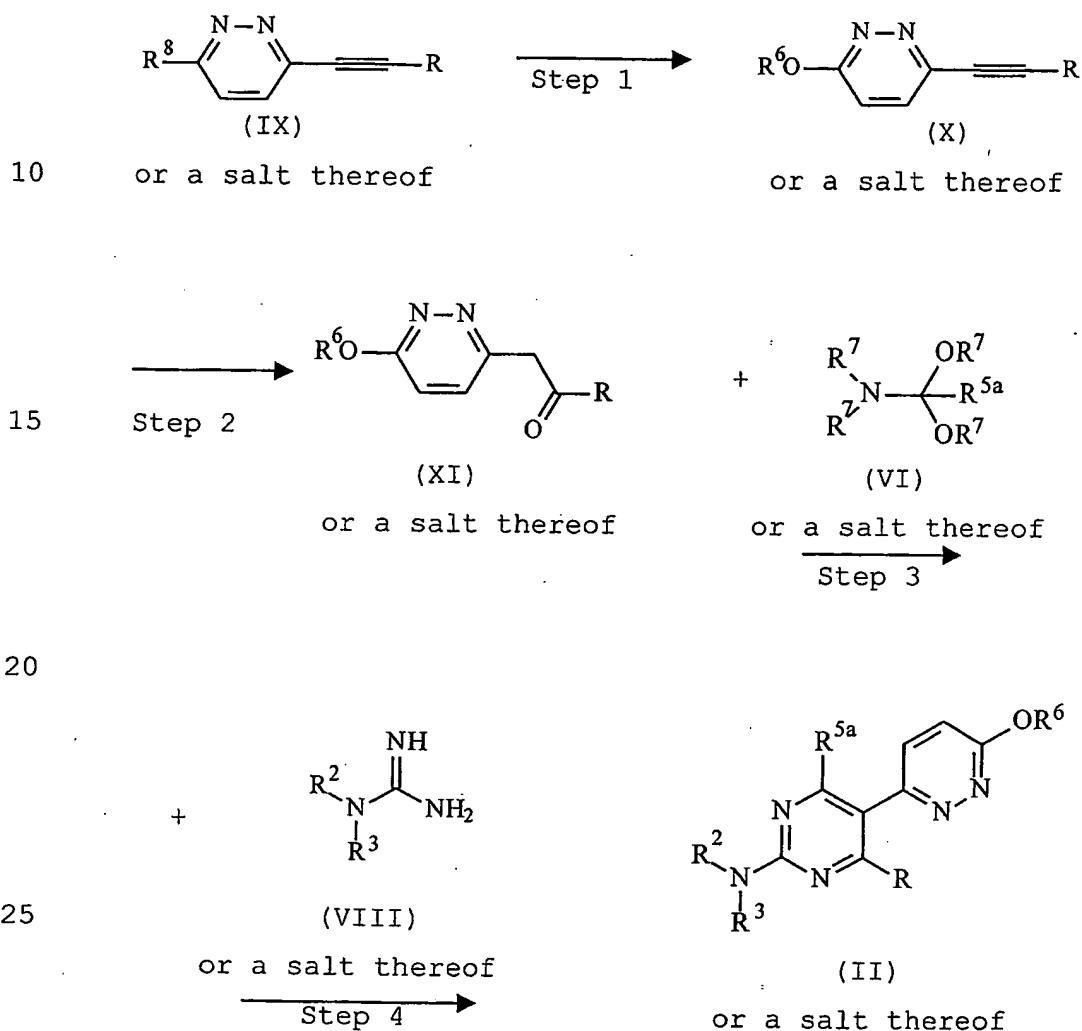
R¹⁴ is optionally substituted lower alkyl;

M is metal; and

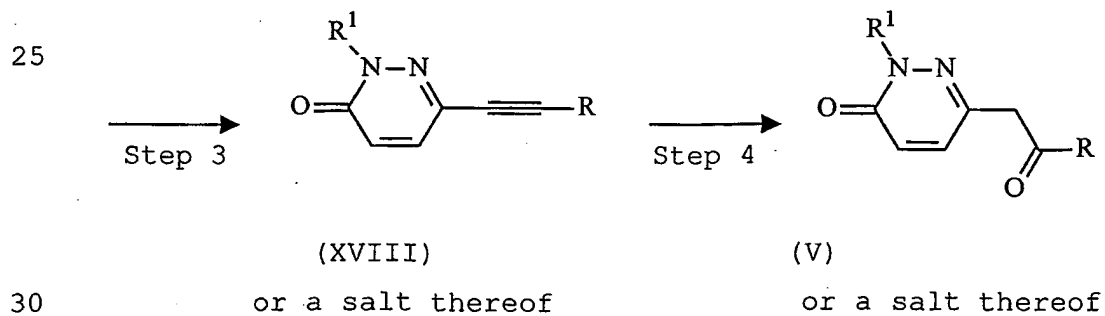
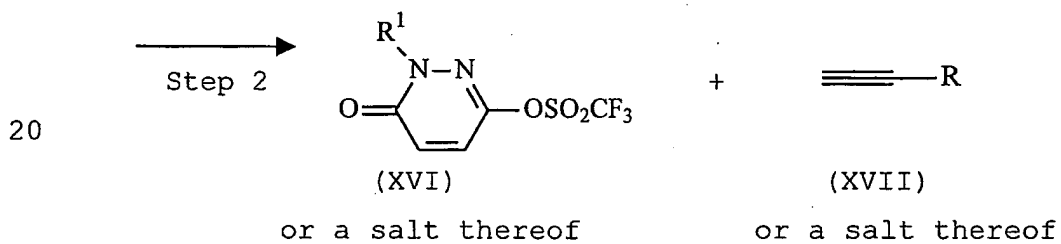
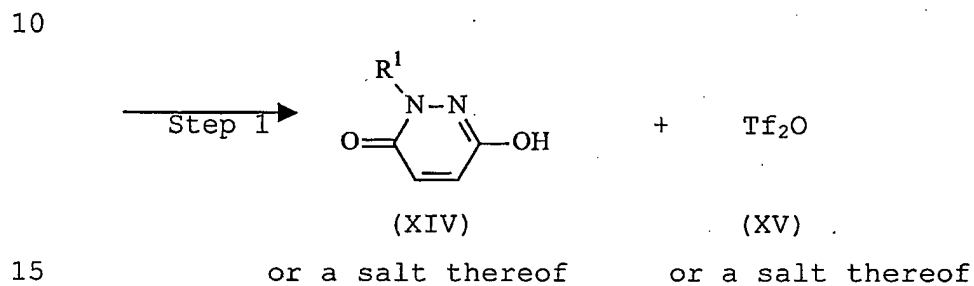
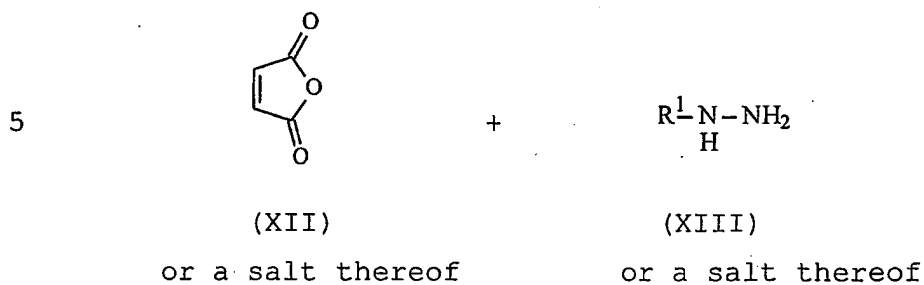
Y¹, Y², Y⁶, Y⁷, Y⁸ and Y⁹ are each a leaving group.

The starting compound(II) or a salt thereof is novel and can be prepared, for example, by the following reaction schemes.

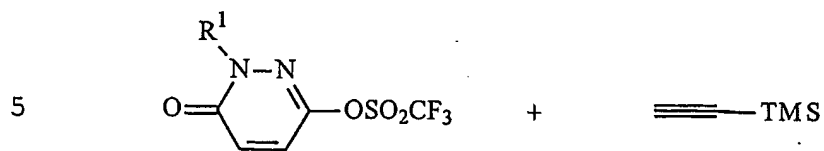
5 Process A



wherein R, R², R³, R^{5a}, R⁶ and R⁷ are as defined above, and R⁸ is arylsulfonyl which may have one or more suitable substituent(s);

Process B

wherein R and R¹ are as defined above, and
Tf₂O is trifluoromethanesulfonic anhydride.

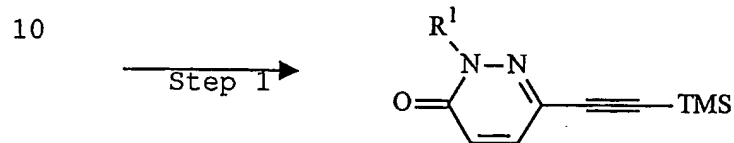
Process C

(XVI)

(XIX)

or a salt thereof

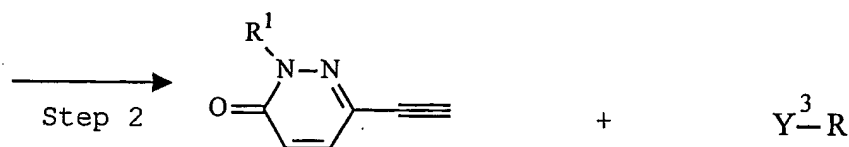
or a salt thereof



(XX)

or a salt thereof

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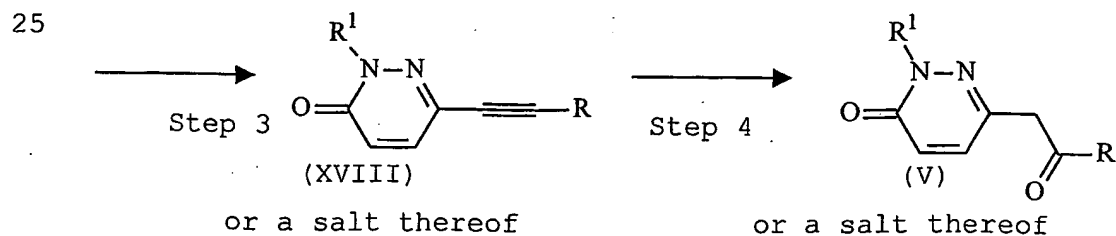
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(XXI)

(XXII)

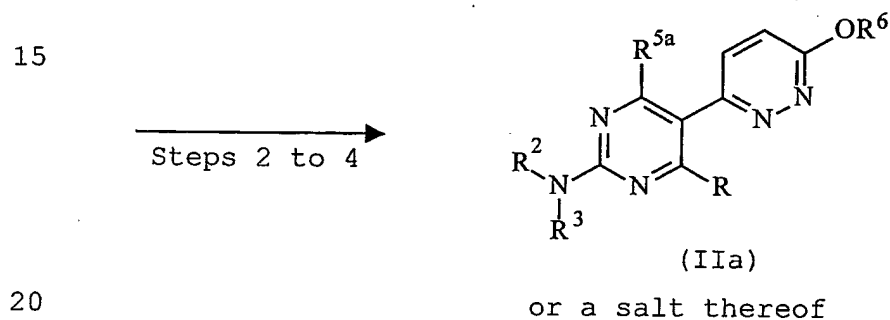
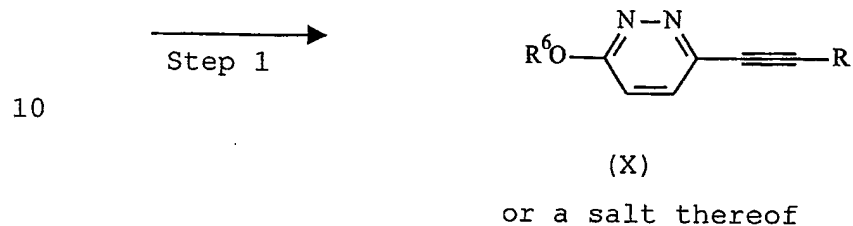
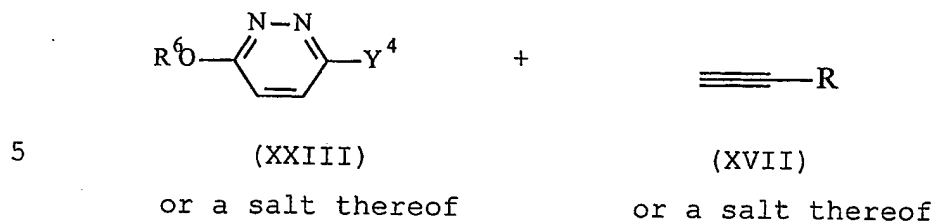
or a salt thereof

or a salt thereof



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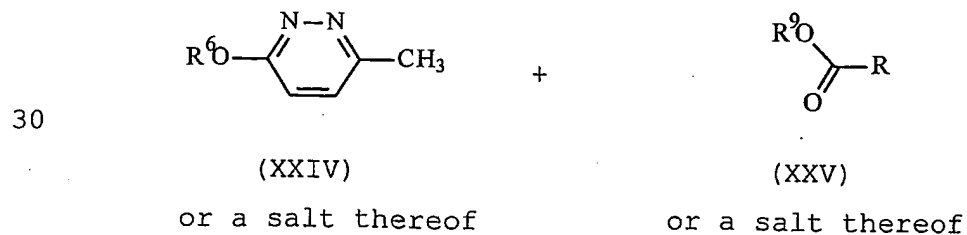
wherein R and R¹ are as defined above,Y³ is a leaving group, and TMS is trimethylsilyl.

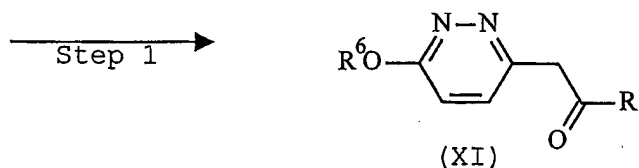
Process D

wherein R, R², R³, R^{5a} and R⁶ are as defined above,
Y⁴ is a leaving group, and

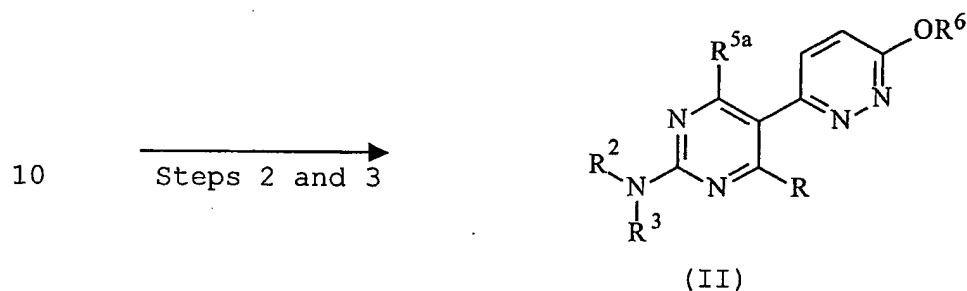
Steps 2 to 4 in Process D are as same as those of Process A.

25

Process E



or a salt thereof



or a salt thereof

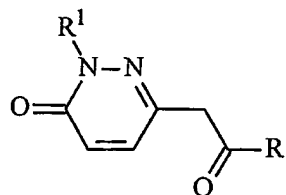
wherein R, R², R³, R^{5a} and R⁶ are as defined above,

R⁹ is lower alkyl, and

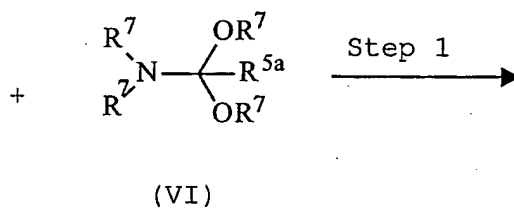
Steps 2 and 3 in Process E are as same as Steps 3 and 4 of Process A respectively.

Process F

20

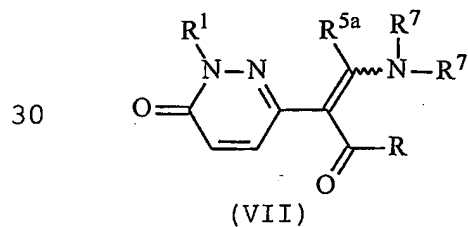


or a salt thereof

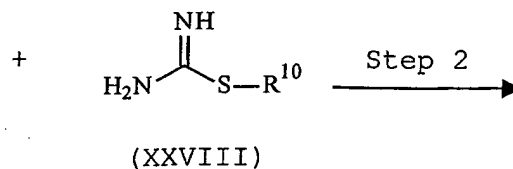


or a salt thereof

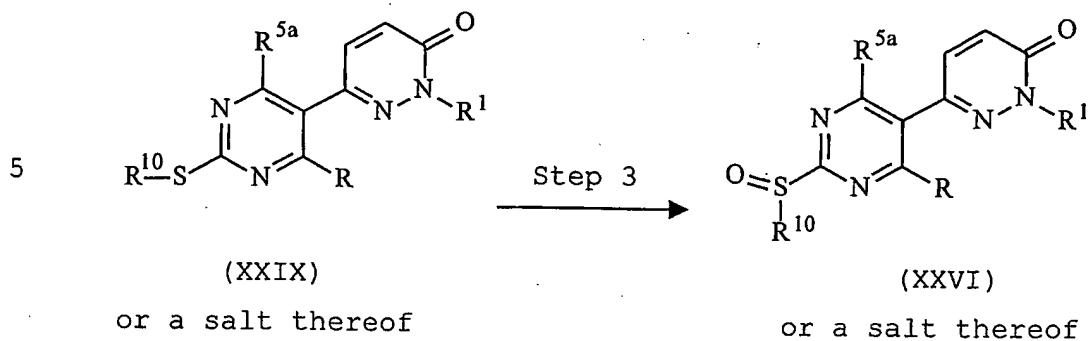
25



or a salt thereof

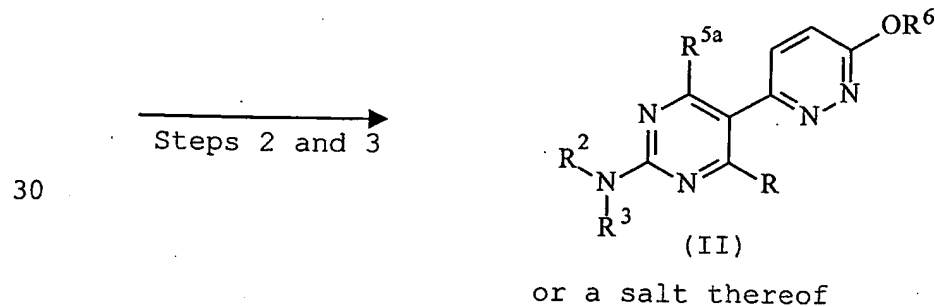
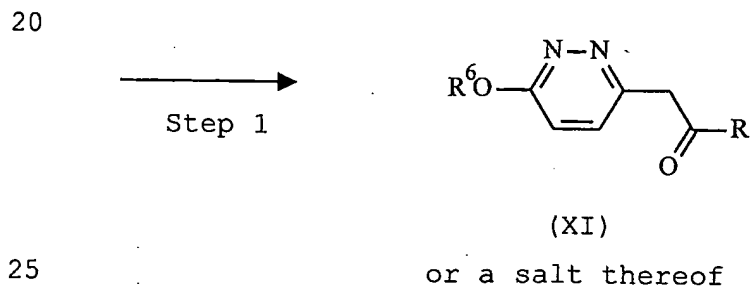
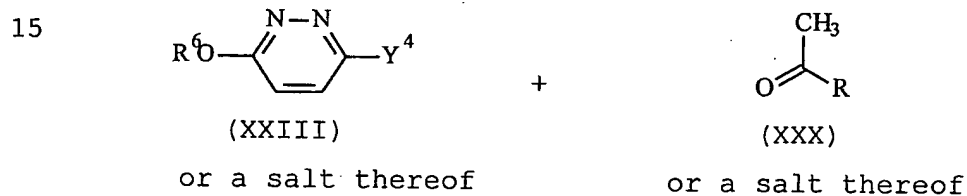


or a salt thereof



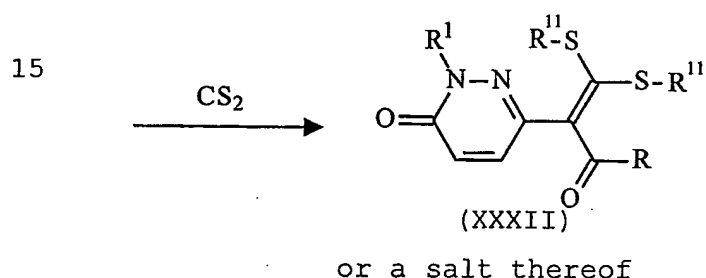
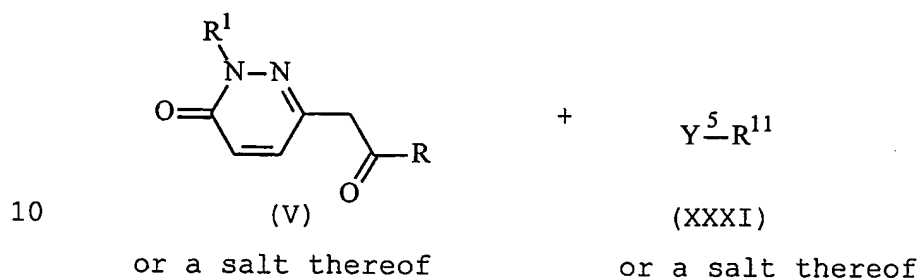
10 wherein R, R¹, R^{5a}, R⁷ and R¹⁰ are as defined above, and Step 1 in Process F is as same as Step 1 of Process 4.

Process G



wherein R, R², R³, R^{5a}, R⁶ and Y⁴ are as defined above, and Steps 2 and 3 in Process G are as same as Steps 3 and 4 of Process A respectively.

5 Process H



wherein R, R¹ and R¹¹ are as defined above, and Y⁵ is a leaving group.

In addition to the processes as mentioned above, the object
25 compound (I) and a salt thereof can be prepared, for example,
according to the procedures as illustrated in Examples in the
present specification or in a manner similar thereto.

The starting compounds can be prepared, for example, according to the procedures as illustrated in Preparations 30 in the present specification or in a manner similar thereto.

The object compound (I) and a salt thereof can be prepared according to the methods as shown in Preparations or Examples, or in a manner similar thereto.

It is to be noted that the object compound (I) may include the geometrical isomer(s) due to the double bond(s) and/or the stereo isomer(s) due to the asymmetric carbon atom(s). In this regard, one isomer can be converted to another according to a conventional method in this field of the art.

It is also to be noted that the solvating form of the compound (I) (e.g. hydrate, etc.) and any form of the crystal of the compound (I) are included within the scope of the present invention.

Suitable salts of the object compound (I) are conventional pharmaceutically acceptable ones and include a metal salt such as an alkali metal salt (e.g. sodium salt, potassium salt, etc.) and an alkaline earth metal salt (e.g. calcium salt, magnesium salt, etc.), an ammonium salt, an organic base salt (e.g. trimethylamine salt, triethylamine salt, pyridine salt, picoline salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.), an organic acid salt (e.g. acetate, trifluoroacetate, maleate, tartrate, fumarate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, etc.), an inorganic acid salt (e.g. hydrochloride, hydrobromide, hydriodide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. arginine, aspartic acid, glutamic acid, etc.), and the like.

Suitable examples and illustrations of the various definitions which the present invention includes within the scope thereof and which appear in the above and following description in the present specification are explained in detail as follows.

The term "lower" is intended to mean 1 to 6 carbon atom(s) unless otherwise indicated.

Suitable "lower alkyl" may include straight or branched ones such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl or the like, in which the preferred

one may be methyl, ethyl, propyl, isopropyl, isobutyl or tert-butyl.

Suitable "lower alkenyl" may include straight or branched ones such as vinyl, 1-propenyl, allyl, butenyl, pentenyl, hexenyl, or the like, in which the preferred one may be allyl.

Suitable "lower alkynyl" may include straight or branched ones such as ethynyl, propynyl, butynyl, or the like, in which the preferred one may be propynyl.

Suitable "lower alkoxy" may include straight or branched ones such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, isopentyloxy, hexyloxy or the like.

Suitable "cyclo(lower)alkyl" may be cyclo(C3-C8)alkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or the like, in which the preferred one may be cyclopropyl, cyclobutyl or cyclohexyl.

Said "cyclo(lower)alkyl" may be interrupted by an oxygen atom, in which the preferred one may be saturated 3-8-membered heteromonocyclic group containing an oxygen atom such as tetrahydrofuryl or tetrahydropyryl.

Suitable "acyl" may include "optionally substituted carbonyl" such as carboxy, optionally substituted lower alkanoyl, optionally substituted lower alkoxy carbonyl, lower cycloalkanoyl, optionally substituted benzoyl, pyridinyl carbonyl or optionally substituted carbamoyl, or the like.

Suitable examples of aforesaid "lower alkanoyl" may include formyl, acetyl, propionyl, isopropionyl, butyryl, isobutyryl, tert-butyryl, valeryl, isovaleryl, pivaloyl, hexanoyl or the like, in which the preferred one may be (C1-C4)alkanoyl and the more preferred one may be acetyl propionyl, isopropionyl, butyryl, isobutyryl, tert-butyryl,.

Suitable substituent of aforesaid "substituted lower

alkanoyl" may include lower alkoxy (e.g. methoxy etc.), or the like.

Suitable examples of aforesaid "lower cycloalkanoyl" may be cyclopropanoyl, cyclobutanoyl, cyclopentanoyl, cyclohexanoyl, in which the preferred one is cyclopropanoyl, cyclohexanoyl.

Suitable examples of aforesaid "optionally substituted lower alkoxy carbonyl" may be methoxycarbonyl, ethoxycarbonyl, tert-butoxycarbonyl, trichloroethoxycarbonyl, or the like.

Suitable examples of aforesaid "optionally substituted benzoyl" may include benzoyl, halobenzoyl (e.g. fluorobenzoyl, chlorobenzoyl, etc.), lower alkyl benzoyl (e.g. toluoyl, etc.), lower alkoxybenzoyl (e.g. methoxybenzoyl, etc.), trihalo(lower)alkyl benzoyl (e.g. trifluoromethoxybenzoyl, etc.), or the like.

Suitable examples of aforesaid "optionally substituted carbamoyl" may include carbamoyl or N-substituted carbamoyl such as N-(lower)alkylcarbamoyl, N-cyclo(lower)alkylcarbamoyl, N,N-di(lower)alkylcarbamoyl, or the like, in which the preferred examples of "optionally substituted carbamoyl" may be carbamoyl, methylcarbamoyl, dimethylcarbamoyl, cyclopropylcarbamoyl, or the like.

Suitable "aryl" may include phenyl, naphthyl, indenyl, anthryl, or the like, in which the preferred one may be (C6-C10) aryl, and the more preferred one may be phenyl.

Suitable "heterocyclic group" may be saturated or unsaturated monocyclic or polycyclic heterocyclic groups containing at least one hetero atom selected from among oxygen, sulfur and nitrogen, and may be optionally substituted with lower alkyl such as methyl.

Preferable examples of "heterocyclic group" are described in the following.

3- through 8-membered unsaturated heteromonocyclic groups

containing 1 through 4 nitrogen atom(s), such as pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl (also referred to as pyridyl), and its N-oxide, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl (e.g. 1H-1,2,4-triazolyl, 5 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g. 1H-tetrazolyl, 2H-tetrazolyl, etc.), dihydrotriazinyl (e.g. 4,5-dihydro-1,2,4-triazinyl, 2,5-dihydro-1,2,4-triazinyl, etc.), etc.;

3- through 8-membered saturated heteromonocyclic groups
10 containing 1 through 4 nitrogen atom(s), such as pyrrolidinyl, imidazolidinyl, piperidyl (e.g. piperidino, etc.), piperazinyl, etc.;

unsaturated condensed heterocyclic groups containing 1
through 5 nitrogen atom(s), such as indolyl, isoindolyl,
15 indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridyl, tetrazolopyridazinyl (e.g. tetrazolo[1,5-b]pyridazinyl etc.), dihydrotriazolopyridazinyl, etc.;

3- through 8-membered unsaturated heteromonocyclic groups
20 containing 1 or 2 oxygen atoms and 1 through 3 nitrogen atom(s), such as oxazolyl, isoxazolyl, oxadiazolyl (e.g. 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

3- through 8-membered saturated heteromonocyclic groups
25 containing 1 or 2 oxygen atom(s) and 1 through 3 nitrogen atoms, such as morpholinyl, oxazolidinyl (e.g. 1,3-oxazolidinyl etc.), etc.;

unsaturated condensed heterocyclic groups containing 1 or
2 oxygen atom(s) and 1 through 3 nitrogen atom(s), such as
30 benzoxazolyl, benzoxadiazolyl, etc.;

3- through 8-membered unsaturated heteromonocyclic groups
containing 1 or 2 sulfur atom(s) and 1 through 3 nitrogen atom(s),
such as 1,3-thiazolyl, 1,2-thiazolyl, thiazolinyl, thiadiazolyl

(e.g. 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, 1,2,3-thiadiazolyl), etc.;

3- through 8-membered saturated heteromonocyclic groups containing 1 or 2 sulfur atom(s) and 1 through 3 nitrogen atom(s),
5 such as thiazolidinyl etc.;

3- through 8-membered unsaturated heteromonocyclic groups containing 1 sulfur atom, such as thienyl etc.;

unsaturated condensed heterocyclic groups containing 1 or 2 sulfur atoms and 1 through 3 nitrogen atom(s), such as
10 benzothiazolyl, benzothiadiazolyl, etc.;

3- through 8-membered unsaturated heteromonocyclic groups containing 1 or 2 oxygen atom(s), such as furyl, pyranyl, dioxolyl, etc.;

3- through 8-membered saturated heteromonocyclic groups containing 1 or 2 oxygen atom(s), such as oxolanyl, tetrahydropyranyl (e.g. tetrahydro-2H-pyran-2-yl etc.), dioxolanyl, etc.; and
15

unsaturated condensed heterocyclic groups containing 1 or 2 oxygen atom(s), such as isobenzofuranyl, chromenyl (e.g. 2H-chromen-3-yl etc.), dihydrochromenyl (e.g. 3,4-dihydro-2H-chromen-4-yl etc.), etc.
20

The particularly preferred example of said "heterocyclic group" may include pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridinyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl, furyl, thienyl, thiazolyl, dimethylthiazolyl, morpholinyl, pyrrolidinyl, piperidinyl, piperazinyl, methylpiperazinyl, tetrahydro-2H-pyranyl, benzimidazolyl, 1,3(2H)-dioxoisindolinyl.
25

Suitable "N-containing heterocyclic group" may be aforesaid "heterocyclic group", in which said group contains at least one N atom in its ring members, and may be optionally substituted with lower alkyl such as methyl.
30

Preferable examples of "N-containing heterocyclic group"

may include pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl, benzimidazolyl, etc.

Suitable "halogen" may be fluoro, chloro, bromo and iodo, in which the preferred one may be fluoro or bromo.

- 5 Suitable "trihalo(lower)alkyl" may include trifluoromethyl, trichloromethyl and tribromomethyl, in which more preferred one is trifluoromethyl.

Suitable "metal" may include magnesium, zinc, or the like.

- 10 Suitable "a leaving group" may include halogen as mentioned above, hydroxy, acyloxy such as alkanoyloxy (e.g. acetoxy, propionyloxy, etc.), sulfonyloxy (e.g. mesyloxy, tosyloxy, etc.), or the like.

- 15 Suitable "arylsulfonyl" may include phenylsulfonyl, tolylsulfonyl, naphthylsulfonyl and the like, and said "arylsulfonyl" may have one or more (preferably 1 to 3) suitable substituent(s) such as aforesaid lower alkoxy, aforesaid halogen, or the like.

- 20 Suitable examples of the substituent of "optionally substituted hydroxy" may include optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group or the like.

- 25 Preferable examples of the substituent of "optionally substituted hydroxy" may include hydroxy, methoxy, ethoxy, propoxy, isopropoxy, allyloxy, propynyloxy, cyclobutoxy, cyclohexyloxy, hydroxyethoxy, methoxyethoxy, carboxymethoxy, aminoethoxy, dimethylaminoethoxy, fluoroethoxy, carbamoylmethoxy, methylcarbamoylmethoxy, dimethylcarbamoylmethoxy, cyclopropylcarbamoylmethoxy, methoxycarbonylmethoxy, tert-butoxycarbonylmethoxy, 30 acetylmethoxy, benzoylmethoxy, phenoxy, benzyloxy, pyridinylmethoxy, pyridinyloxy, tetrahydro-2H-pyranyloxy or 1,3(2H)-dioxoisindolinylethoxy.

Suitable examples of the substituent of "optionally

substituted amino which may form N-containing heterocyclic group" may include optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl, heterocyclic group or the like, and they may be combined together with N atom
5 to which they are attached to form N-containing heterocyclic group.

Preferable examples of "optionally substituted amino which may form N-containing heterocyclic group" may include amino, methylamino, ethylamino, propylamino, isopropylamino,
10 tert-butylamino, allylamino, cyclopropylamino, hydroxyethylamino, methoxyethylamino, aminoethylamino, dimethylaminoethylamino, carbamoylmethylamino, amidinoamino, anilino, benzylamino, pyridinylamino, pyridinylmethylamino, furylmethylamino, dimethylthiazolylamino, dimethylamino,
15 benzyl(methyl)amino, pyrrolidinyl, piperidinyl, morpholino, piperazinyl, methylpiperazinyl, imidazolyl, triazolyl or benzimidazolyl.

Suitable examples of the substituent of "optionally substituted lower alkyl" may include halo, trihalo, hydroxy,
20 lower alkoxy, optionally substituted amino, acyl, aryl, heterocyclic group or the like.

Preferable examples of "optionally substituted lower alkyl" may include methyl, ethyl, propyl, isopropyl, isobutyl, tert-butyl, fluoroethyl, trifluoromethyl, hydroxyethyl,
25 hydroxyisopropyl, methoxyethyl, methoxyisopropyl, carboxymethyl, aminoethyl, dimethylaminoethyl, carbamoylmethyl, methylcarbamoylmethyl, dimethylcarbamoylmethyl, cyclopropylcarbamoylmethyl, methoxycarbonylmethyl, tert-butoxycarbonylmethyl,
30 acetylmethyl, benzoylmethyl, benzyl, pyridinylmethyl, pyridinylethyl, furylmethyl or 1,3(2H)-dioxoisindolinylethyl.

Suitable examples of the substituent of "optionally

substituted lower alkoxy" may include halo, trihalo, lower alkoxy, optionally substituted amino, or heterocyclic group or the like.

Preferable examples of "optionally substituted lower alkoxy"
5 may include methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentyloxy, isopentyloxy, hexyloxy, fluoroethoxy, fluoropropoxy, trichloroethoxy, methoxyethoxy, dimethylaminoethoxy or morpholinylethoxy.

Suitable examples of the substituent of "optionally
10 substituted aryl", "optionally substituted phenyl" or "optionally substituted benzoyl" may include halo, hydroxy, lower alkyl, optionally substituted lower alkoxy, trihalo(lower)alkyl, lower alkylthio, lower alkylsulfinyl or lower alkylsulfonyl, or the like.

15 Preferable examples of "optionally substituted aryl" may include phenyl which may be substituted with fluoro, bromo, chloro, hydroxy, methyl, trifluoromethyl, methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, isopentyloxy, hexyloxy, methoxyethoxy, fluoroethoxy, fluoropropoxy,
20 dimethylaminoethoxy, morpholinylethoxy, methylthio, methylsulfinyl or methylsulfonyl.

Suitable examples of the substituent of "optionally substituted mercapto" may include lower alkyl, lower alkanoyl, aryl, or the like.

25 Preferable examples of "optionally substituted mercapto" may include methylthio, acetylthio or phenylthio.

The processes for preparing the object aminopyrimidine compound(I) are explained in detail in the following.

30 Process 1

The compound (Ia) or a salt thereof can be prepared by subjecting the compound (II) or a salt thereof to hydrolysis.

Suitable salt of the compound (II) can be referred to an

acid addition salt as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method.

The hydrolysis is preferably carried out in the presence
5 of a base or an acid including Lewis acid.

Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), the hydroxide or carbonate or hydrogencarbonate thereof,
10 trialkylamide (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]-octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

Suitable acid includes an organic acid (e.g. formic acid,
15 acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

The elimination using Lewis acid such as BBr₃, BCl₃, BF₃,
20 AlCl₃, TiCl₄ or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

The reaction is usually carried out in a solvent such as water, an alcohol (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride,
25 ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

A liquid base or acid can be also used as the solvent. The reaction temperature is not critical and the reaction is
30 usually carried out under cooling to heating.

Process 2

The compound (Ib) or a salt thereof can be prepared by reacting the compound (Ia) or a salt thereof with the compound

(III) or a salt thereof.

Suitable salt of the compound (Ia) can be referred to an acid addition salt as exemplified for the compound (I).

Suitable salt of the compound (III) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylene chloride, ethylene chloride, formamide, N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When the compound (III) is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride, etc.), organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate, potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When Y¹ is -OH, activation of OH with triphenylphosphine and the like may be necessary.

Process 3

The compound (Id) or a salt thereof can be prepared by reacting the compound (Ic) or a salt thereof with the compound (IV) or a salt thereof.

Suitable salt of the compound (Ic) and (IV) can be referred
5 to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylenechloride, ethylenechloride, formamide, N,N-dimethylformamide, N,N-dimethylacetamide, methanol,
10 ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, pyridine or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic solvents may be used in a mixture with water. When
15 the compound (IV) is in liquid, it can also be used as a solvent.

The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride
20 (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction
25 is usually carried out at ambient temperature, under warming or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate,
30 potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When Y² is -OH, activation of OH with triphenylphosphine

and the like may be necessary.

Process 4

5 The compound (Ie) or a salt thereof can be prepared by
subjecting the compound (V) or a salt thereof to formation
reaction of pyrimidine ring.

Suitable salt of the compound (V) and (VI) can be referred
to the ones as exemplified for the compound (I).

10 Suitable salt of the compound (VIII) can be referred to
an acid addition salt as exemplified for the compound (I),
in which the preferred one is hydrochloride.

This reaction can be carried out by reacting the compound
(V) or a salt thereof with the compound (VI) or a salt thereof
(Step 1), and further reacting with the compound (VIII) or
a salt thereof (Step 2).

15 The reactions may be carried out in a conventional solvent
such as water, alcohol (e.g. methanol, ethanol, etc.), acetone,
dioxane, acetonitrile, chloroform, methylenechloride, ethylene
chloride, tetrahydrofuran, ethyl acetate,
N,N-dimethylformamide, pyridine or any other organic solvent
20 which does not adversely affect the reaction. These conventional
solvents may also be used in a mixture with water. In case
of Step 1, the compound VI can also be used as a single solvent.
The reaction is preferably conducted in the presence of a base,
for example, inorganic base such as alkali metal hydroxide
25 (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali
metal carbonate (e.g. sodium carbonate, potassium carbonate,
etc.), alkali metal bicarbonate (e.g. sodium hydrogen carbonate,
potassium hydrogen carbonate, etc.), alkali metal hydride (e.g.
sodium hydride), alkali metal alkoxide (e.g. MeONa, EtONa,
30 t-BuOK, etc.) organic base such as trialkylamine (e.g.
trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine,
etc.), and the like.

The reaction temperature is not critical, and the reaction

is usually carried out at ambient temperature, under warming or under heating.

Process 5

The compound (I) or a salt thereof can be prepared by reacting
5 the compound (XXVI) or a salt thereof with the compound (XXVII) or a salt thereof.

Suitable salt of the compound (XXVI) and (XXVII) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such
10 as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction is preferably conducted in the presence of
15 a base, for example, inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkali metal carbonate, alkali metal bicarbonate, alkali metal hydride (e.g. sodium hydride), alkali metal alkoxide (e.g. EtONa, t-BuOK, etc.) organic base such as trialkylamine (e.g. trimethylamine,
20 triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

25 The reaction can be carried out by the method disclosed in Example 17 mentioned later or the similar manner thereto.

Process 6

The compound (If) or a salt thereof can be prepared by reacting the compound (XXXII) or a salt thereof with the compound
30 (VIII) or a salt thereof.

Suitable salt of the compound (XXXII) and (VIII) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such

as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

5 The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

 The reaction can be carried out by the method disclosed in Example 78 mentioned later or the similar manner thereto.

10 Process 7

 The compounds (Ig) and (Ih) or salts thereof can be prepared by oxidizing the compound (If) or a salt thereof.

 The oxidation is carried out in the presence of an oxidizer such as 3-chloroperbenzoic acid.

15 Suitable salt of the compound (If) can be referred to the ones as exemplified for the compound (I).

 The present reaction may be carried out in a solvent such as dioxane, chloroform, methylene chloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile,

20 N,N-dimethylformamide; N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

 The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

25 The reaction can be carried out by the method disclosed in Example 79 mentioned later or the similar manner thereto.

Process 8

 The compound (Ii) or a salt thereof can be prepared by reacting the compound (Ig) or a salt thereof with the compound (XXXIII) or a salt thereof.

30 This reaction can be carried out in the same manner as in the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction

temperature, etc.) can be referred to those of Process 5.

The reaction can be carried out by the method disclosed in Example 80, 81, 85 and 89 mentioned later or the similar manner thereto.

5 Process 9

The compound (Ii) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (XXXIII) or a salt thereof.

10 This reaction can be carried out in the same manner as in the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 5.

The reaction can be carried out by the method disclosed in Example 91, 93, 94 and 95 mentioned later or the similar
15 manner thereto.

Process 10

The compound (Ij) or a salt thereof can be prepared by reacting the compound (Ig) or a salt thereof with the compound (XXXIV) or a salt thereof.

20 This reaction can be carried out in the same manner as in the aforementioned Process 5, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 5.

The reaction can be carried out by the method disclosed
25 in Example 105, 114, 115, 118, 119, 120, 128, 130 and 133 mentioned later or the similar manner thereto.

Process 11

The compound (Ik) or a salt thereof can be prepared by reacting the compound (If) or a salt thereof with urea hydrogen
30 peroxide addition compound.

This reaction can be carried out by the method disclosed in Example 140 mentioned later or the similar manner thereto.

Process 12

The compound (Il) or a salt thereof can be prepared by reacting the compound (Ik) or a salt thereof with the compound (XXXV) or a salt thereof.

Suitable salt of the compound (Ik) and (XXXV) can be referred to the ones as exemplified for the compound (I).

The present reaction may be carried out in a solvent such as dioxane, chloroform, methylenechloride, 1,2-dichloroethane, tetrahydrofuran, pyridine, acetonitrile, N,N-dimethylformamide, N,N-dimethylacetamide or any other solvent which does not adversely affect the reaction.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming or under heating.

This reaction can be carried out by the method disclosed in Example 159 mentioned later or the similar manner thereto.
Process 13

The compound (In) or a salt thereof can be prepared by reacting the compound (Im) or a salt thereof with the compound (XXXVI) or a salt thereof.

This reaction can be carried out in the same manner as in the aforementioned Process 3, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 3.

The reaction is preferably conducted in the presence of N-ethyl-N,N-diisopropylamine.

The reaction can be carried out by the method disclosed in Example 178 mentioned later or the similar manner thereto.
Process 14

The compound (Ip) or a salt thereof can be prepared by subjecting the compound (Io) or a salt thereof to elimination reaction of alkyl group.

Suitable salts of the compound (Io) can be referred to the ones as exemplified for the compound (I).

This reaction is carried out in accordance with a conventional method such as hydrolysis.

The hydrolysis is preferably carried out in the presence of a base or an acid including Lewis acid.

5 Suitable base includes an inorganic base and an organic base such as an alkali metal (e.g. sodium, potassium, etc.), an alkaline earth metal (e.g. magnesium, calcium, etc.), hydroxide or carbonate or bicarbonate thereof, trialkylamine (e.g. trimethylamine, triethylamine,
10 N-ethyl-N,N-diisopropylamine, etc.), hydrazine, picoline, 1,5-diazabicyclo[4.3.0]non-5-ene, 1,4-diazabicyclo[2.2.2]octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or the like.

 Suitable acid includes an organic acid (e.g. formic acid,
15 acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, hydrogen chloride, hydrogen bromide, etc.).

 The elimination using Lewis acid (e.g. aluminium chloride,
20 boron tribromide, boron trichloride, titanium trichloride, tin tetrachloride, etc.) or the like is preferably carried out in the presence of cation trapping agents (e.g. anisole, phenol, etc.).

 The reaction is usually carried out in a solvent such as
25 water, alcohol (e.g. methanol, ethanol, isopropyl alcohol, etc.), tetrahydrofuran, dioxane, toluene, methylene chloride, ethylene dichloride, chloroform, N,N-dimethylformamide, N,N-dimethylacetamide, or any other organic solvents which do not adversely affect the reaction, or a mixture thereof.

30 A liquid base or acid can be also used as the solvent.

 The reaction of this process can be also carried out according to a conventional reduction method employed in this field of the art (e.g. chemical reduction, catalytic reduction, etc.).

The reaction temperature is not critical and the reaction is usually carried out at ambient temperature, under warming or under heating.

Process 15

- 5 The compound (Iq) or a salt thereof can be prepared by reacting the compound (Ip) or a salt thereof with the compound (XXXVII) or a salt thereof.

Suitable salt of the compound (Ip) can be referred to an acid addition salt as exemplified for the compound (I).

- 10 Suitable salt of the compound (XXXVII) can be referred to the ones as exemplified for the compound (I).

- The present reaction may be carried out in a solvent such as water, phosphate buffer, acetone, chloroform, acetonitrile, nitrobenzene, methylenechloride, ethylenechloride, formamide,
15 N,N-dimethylformamide, N,N-dimethylacetamide, methanol, ethanol, sec-butanol, amyl alcohol, diethyl ether, dioxane, tetrahydrofuran, dimethyl sulfoxide, or any other organic solvent which does not adversely affect the reaction, preferably in ones having strong polarities. Among the solvents, hydrophilic
20 solvents may be used in a mixture with water. When the compound (XXXVII) is in liquid, it can also be used as a solvent. The reaction is preferably conducted in the presence of a base, for example, inorganic base such as alkali metal hydroxide, alkali metal carbonate, alkali metal bicarbonate, alkali metal
25 hydride (e.g. sodium hydride, etc.), organic base such as trialkylamine (e.g. trimethylamine, triethylamine, N-ethyl-N,N-diisopropylamine, etc.), and the like.

- The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature, under warming
30 or under heating.

The present reaction is preferably carried out in the presence of alkali metal halide (e.g. sodium iodide, potassium iodide, etc.), alkali metal thiocyanate (e.g. sodium thiocyanate,

potassium thiocyanate, etc.), di(lower)alkyl azodicarboxylate (e.g. diethyl azodicarboxylate, diisopropyl azodicarboxylate, etc.) or the like.

When Y^8 is -OH, activation of OH with triphenylphosphine and the like may be necessary.

Process 16

The compound (Ir) or a salt thereof can be prepared by reacting the compound (Ih) or a salt thereof with the compound (XXXVIII) or a salt thereof.

10 This reaction can be carried out by the method disclosed in Example 253 mentioned later or the similar manner thereto.

Process A

The reactions of steps 1 and 2 can be respectively carried out by the methods disclosed in Preparations 1 and 2 mentioned later or the similar manners thereto.

The reactions of steps 3 and 4 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process B

The reactions of steps 1 to 4 can be respectively carried out by the methods disclosed in Preparations 6 to 9 mentioned later or the similar manners thereto.

25 Process C

The reactions of steps 1 to 4 can be respectively carried out by the methods disclosed in Preparations 10 to 12 and 9 mentioned later or the similar manners thereto.

Process D

30 The reaction of Step 1 can be carried out by the method disclosed in Preparation 13 mentioned later or the similar manners thereto.

The reaction of step 2 can be carried out by the method

disclosed in Preparation 2 mentioned later or the similar manners thereto.

The reactions of steps 3 and 4 can be carried out in the same manner as in the aforementioned Process 4, and therefore
5 the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process E

The reaction of Step 1 can be carried out by the method
10 disclosed in Preparation 15 mentioned later or the similar manners thereto.

The reactions of steps 2 and 3 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents to be used and the reaction conditions (e.g.,
15 solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process F

The reaction of step 1 can be carried out in the same manner as in the aforementioned Process 4, and therefore the reagents
20 to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

The reaction of Step 2 can be carried out by the method disclosed in Preparation 20 mentioned later or the similar manners thereto.

25 The oxidation reaction of step 3 can be carried out by the method disclosed in Preparation 21 mentioned later or the similar manners thereto.

Process G

The reaction of Step 1 can be carried out by the method
30 disclosed in Preparation 43 mentioned later or the similar manners thereto.

The reactions of steps 2 and 3 can be carried out in the same manner as in the aforementioned Process 4, and therefore

the reagents to be used and the reaction conditions (e.g., solvent, reaction temperature, etc.) can be referred to those of Process 4.

Process H

5 The compound (XXXII) or a salt thereof can be prepared by reacting the compound (V) or a salt thereof with the compound (XXXI) or a salt thereof.

 This reaction can be carried out by the method disclosed in Preparation 77 mentioned later or the similar manners thereto.

10

 The object compound (I) of the present invention is an adenosine antagonist and possesses the various pharmacological actions as stated before.

 In order to show the usefulness of the compound (I) of the
15 present invention, the pharmacological test result of the representative compound of the present invention is shown in the following.

[I] Test compound

20 6-(2-Amino-4-phenyl-5-pyrimidinyl)-3(2H)-pyridazinone (Example 1)

 6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-ethyl-3(2H)-pyridazinone (Example 4)

25 N-[5-(1-Isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]acetamide (Example 7)

 2-Isopropyl-6-{4-phenyl-2-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-3(2H)-pyridazinone (Example 18)

 6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (Example 47)

30 6-(2-Amino-4-fluoro-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (Example 136)

 6-{2-Amino-4-[4-(2-methoxyethoxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (Example 212)

[II] Test method

Test 1 : Adenosine antagonistic activity

The adenosine antagonistic activity [K_i (nM)] of the test compound was examined by radioligand binding techniques using
 5 8-cyclopentyl-1,3-dipropylxanthine, [dipropyl-2,3- ^3H (N)]
 ([^3H]DPCPX, 4.5nM) for human A_1 receptor and [^3H]CGS 21680 (20nM)
 for human A_{2a} receptor.

Test 2 : Anticatalepsy activity in Mouse

The test compound (3.2mg/kg) was administered orally with
 10 ddY mice(n=7). Then, haloperidol (0.32mg/kg) was injected
 intraperitoneally 30 min. after the administration of the
 compound. Thirty min. after the injection, the cataleptic
 responses of mice were measured. The forelimbs of each mouse
 were placed on a 3 cm high, 3 mm wide horizontal bar, and the
 15 duration of cataleptic posture was measured for up to 30 sec.

[III] Test result

Test 1 : Adenosine antagonistic activity

20

Table 1

Test compound (Example No.)	Adenosine receptor binding	
	(Ki:nM)	
	A_1	A_{2a}
1	11.35	3.85
25 4	3.14	4.35
7	6.47	2.09
18	10.78	7.38
47	7.74	1.38
136	1.75	1.41
30 212	2.36	1.70

Test 2 : Anticatalepsy activity in Mouse

Table 2

5	Test compound	Manifestation rate of catalepsy
	(Example No.)	(number of mouse)
	1	4/7
	4	0/7
	7	0/7
	18	0/7
10	47	1/7
	136	0/7
	212	0/7

15 The aminopyrimidine compound (I) and a salt thereof of
this invention are useful as adenosine antagonists (especially,
A₁ receptor and A₂ (particularly A_{2a}) receptor dual antagonists)
and for the prevention and/or the treatment of depression,
dementia (e.g. Alzheimer's disease, cerebrovascular dementia,
20 dementia accompanying Parkinson's disease, etc.), Parkinson's
disease, anxiety, pain, cerebrovascular disease, heart failure,
hypertension, circulatory insufficiency, post-resuscitation,
asystole, bradyarrhythmia, electro-mechanical dissociation,
hemodynamic collapse, SIRS (systemic inflammatory response
25 syndrome), multiple organ failure, renal failure (renal
insufficiency), renal toxicity, nephrosis, nephritis, edema,
obesity, bronchial asthma, gout, hyperuricemia, sudden infant
death syndrome, immunosuppression, diabetes, ulcer,
pancreatitis, Meniere's syndrome, anemia, dialysis-induced
30 hypotension, constipation, ischemic bowel disease, ileus,
myocardial infarction, thrombosis, obstruction,
arteriosclerosis obliterans, thrombophlebitis, cerebral
infarction, transient ischemic attack, angina pectoris, and

the like.

The pharmaceutical composition of this invention can be used in the form of a pharmaceutical preparation, for example, in a solid, semisolid or liquid form, which contains the aminopyrimidine compound (I) or a pharmaceutically acceptable salt thereof as an active ingredient in admixture with an organic or inorganic carrier or excipient suitable for rectal, pulmonary (nasal or buccal inhalation), nasal, ocular, external (topical), oral or parenteral (including subcutaneous, intravenous and intramuscular) administrations or insufflation. The active ingredient may be compounded, for example, with the usual non-toxic, pharmaceutically acceptable carriers for tablets, pellets, troches, capsules, suppositories, creams, ointments, aerosols, powders for insufflation, solutions, emulsions, suspensions, and any other form suitable for use. In addition, auxiliary, stabilizing agents, thickening agents, coloring agents and perfumes may be used where necessary. The aminopyrimidine compound (I) or a pharmaceutically acceptable salt thereof is included in a pharmaceutical composition in an amount sufficient to produce the desired aforesaid pharmaceutical effect upon the process or condition of diseases.

For applying the composition to a human being or an animal, it is preferable to apply it by intravenous, intramuscular, pulmonary or oral administration, or insufflation. While the dosage of therapeutically effective amount of the aminopyrimidine compound (I) varies depending on the age and condition of each individual patient to be treated, in the case of intravenous administration, a daily dose of 0.01 - 100 mg of the aminopyrimidine compound (I) per kg weight of a human being or an animal, in the case of intramuscular administration, a daily dose of 0.01 - 100 mg of the aminopyrimidine compound (I) per kg weight of a human being or an animal, and in case of oral administration, a daily dose

of 0.01 - 100 mg of the aminopyrimidine compound (I) per kg weight of a human being or an animal is generally given for the prevention and/or treatment of the aforesaid diseases.

5 The following Preparations and Examples are given for the purpose of illustrating the present invention in more detail.

Preparation 1

A suspension of 3-(phenylethynyl)-6-(phenylsulfonyl)-pyridazine (138.8 g) in MeOH (1.4 l) was cooled in an ice bath.
10 28% NaOMe in MeOH (92 g) was added dropwise to the mixture at 10°C over a period of 10 minutes and the mixture was stirred at 5-10°C for 1 hour and 15 minutes. After the solvent was removed under reduced pressure, the residue was partitioned between EtOAc (1000 ml) and water (500 ml). After an additional
15 extraction with EtOAc (500 ml), the combined extracts were washed with brine (500 ml), dried over anhydrous MgSO₄, and concentrated to give crude material, which was then purified by silica gel column chromatography (n-Hexane:EtOAc, 2:1 v/v) to afford 3-methoxy-6-(phenylethynyl)pyridazine (68.8 g) as
20 colorless crystals.

mp: 98-99°C

IR (Nujol): 2214, 1651 cm⁻¹

NMR (DMSO-d₆, δ): 4.10 (3H, s), 7.30 (1H, d, J=9.1 Hz), 7.46-7.53 (3H, m), 7.64-7.69 (2H, m), 7.86 (1H, d, J=9.1 Hz).

25 ESI/MS: 233 [M+Na]⁺

Preparation 2

To a solution of 3-methoxy-6-(phenylethynyl)pyridazine (24.0 g) in AcOH (360 ml) was added dropwise conc. H₂SO₄ (120 ml) and the mixture was heated to reflux for 4.5 hours. AcOH
30 was removed under reduced pressure and the residue was poured into ice (1 kg). Aqueous NaOH was added to the mixture to neutralize and extracted with EtOAc (x 3). The combined extracts were washed with brine, dried over MgSO₄, and concentrated under

reduced pressure. The crude material was purified by column chromatography on silica-gel (n-Hexane-EtOAc, 1:1 v/v) to give 2-(6-methoxy-3-pyridazinyl)-1-phenylethanone (24.53 g) as yellow crystals.

5 mp: 103-104°C

IR (Nujol): 1678, 1652 cm^{-1}

NMR (CDCl_3 , δ): 4.11 (3H, s), 4.61 (2H, s), 6.95 (1H, d, J = 9.1 Hz), 7.39-7.59 (4H, m), 8.07-8.12 (2H, m).

ESI/MS: 229 $[\text{M}+\text{H}]^+$

10 Preparation 3

A mixture of 2-(6-methoxy-3-pyridazinyl)-1-phenylethanone (1.50 g) and N,N-dimethylformamide dimethylacetal (1.57 g) was heated to reflux for 2.5 hours. The mixture was cooled to ambient temperature, washed with n-hexane (3 times) and
15 dried to give an oil (1.91 g). The oil was dissolved in EtOH, and guanidine hydrochloride (1.26 g) and 28% NaOMe / in MeOH (2.60 g) was added to the mixture, which was then heated to reflux for 2.5 hours. The mixture was poured into ice/water and extracted with EtOAc (x 2). The combined extracts were washed
20 with water and brine, dried over MgSO_4 and concentrated under reduced pressure. The crude material was purified by silica-gel column chromatography (CHCl_3 -MeOH, 50:1 v/v) to give 2-amino-5-(6-methoxy-3-pyridazinyl)-4-phenylpyrimidine (1.36 g) as colorless crystals.

25 IR (Nujol): 3325, 3192, 1653, 1562, 1538 cm^{-1}

NMR ($\text{DMSO}-d_6$, δ): 4.03 (3H, s), 6.99-7.11 (4H, m), 7.25-7.43 (5H, m), 8.49 (1H, s)

ESI/MS: 279 $[\text{M}+\text{Na}]^+$

Elemental Analysis for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}$

30 Calcd.: C, 64.51; H, 4.69; N, 25.08

Found : C, 64.45; H, 4.74; N, 24.93

Preparation 4

5-(6-Methoxy-3-pyridazinyl)-N-methyl-4-phenyl-2-

pyrimidinamine was obtained from
2-(6-methoxy-3-pyridazinyl)-1- phenylethanone,
N,N-dimethylformamide dimethylacetal and 1-methylguanidine
hydrochloride according to a similar manner to that of Preparation

5 3.

NMR (DMSO- d_6 , δ): 2.91 (3H, d, $J=4.8$ Hz), 4.03 (3H, s), 7.02 (1H,
d, $J=9.2$ Hz), 7.09 (1H, d, $J=9.2$ Hz), 7.32-7.52 (6H, m), 8.53 (1H,
brd. s)

ESI/MS: 316 $[M+Na]^+$

10 Preparation 5

5-(6-Methoxy-3-pyridazinyl)-N,N-dimethyl-4-phenyl-2-
pyrimidinamine was obtained from

2-(6-methoxy-3-pyridazinyl)-1- phenylethanone,
N,N-dimethylformamide dimethylacetal and

15 1,1-dimethylguanidine hydrochloride according to a similar
manner to that of Preparation 3.

NMR (DMSO- d_6 , δ): 3.24 (6H, s), 4.03 (3H, s), 7.03 (1H, d, $J=9.2$
Hz), 7.10 (1H, d, $J=9.2$ Hz), 7.31-7.41 (5H, m), 8.59 (1H, s).

ESI/MS: 330 $[M+Na]^+$

20 Preparation 6

To a solution of maleic anhydride (41.57 g) in glacial
acetic acid (310 ml) was added 1-isopropylhydrazine (31.43
g) at ambient temperature. The mixture was heated under reflux
for 5 hours and concentrated under reduced pressure to give
25 a solid. The solid was triturated by isopropyl ether, collected
by filtration, and recrystallized from a mixture of methanol
and isopropyl ether to give

6-hydroxy-2-isopropyl-3(2H)-pyridazinone (60.27 g).

mp: 162-164°C (methanol - isopropyl ether)

30 IR (KBr) : 1504 cm^{-1}

1H NMR ($CDCl_3$, δ): 1.22 (6H, d, $J=6.66$ Hz), 5.03 (1H, 7-plet,
 $J=6.65$ Hz), 6.85 (1H, d, $J=9.62$ Hz), 7.01 (1H, d, $J=9.62$ Hz),

10.95(1H, br.s)

APCI/MS: 155 [M+H]⁺

Elemental Analysis for C₇H₁₀N₂O₂

Calcd.: C, 54.54; H, 6.54; N, 18.17

5 Found : C, 54.72; H, 6.61; N, 18.13

Preparation 7

To a solution of 6-hydroxy-2-isopropyl-3(2H)-pyridazinone (5.00 g) in pyridine (32 ml) was dropwise added trifluoromethanesulfonic anhydride (5.51 ml) under ice-cooling. 10 The mixture was stirred under ice-cooling for one hour and at ambient temperature for 3 hours. Pyridine was removed under reduced pressure to give a residue. The residue was dissolved a mixture of ethyl acetate and water. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated 15 under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 8:2 v/v) to give 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethane- sulfonate as a solid (8.66 g).

mp: 45-46°C (n-hexane)

20 IR (KBr) : 1660, 1587 cm⁻¹

¹H NMR (CDCl₃, δ) : 1.34(6H, d, J=6.62 Hz), 5.23(1H, 7-plet, J=6.61 Hz), 7.04(1H, d, J=9.83 Hz), 7.16(1H, d, J=9.83 Hz)

APCI/MS: 287 [M+H]⁺

Elemental Analysis for C₈H₉F₃N₂O₄S

25 Calcd.: C, 33.57; H, 3.17; N, 9.79

Found : C, 33.80; H, 2.96; N, 9.79

Preparation 8

In the presence of dichlorobis(triphenylphosphine)-palladium(II) (0.42 g) and copper(I) iodide (0.42 g), 30 triethylamine (3.9 ml) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethane- sulfonate (5.73 g), 1-ethynyl-4-fluorobenzene (3.65 g) in dioxane (60 ml) at 75-80°C

for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, water and chloroform were added to the reaction mixture. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 7:3 v/v) to give 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone as a solid (4.22 g).

mp: 105.5-106.5°C (n-hexane)

IR (KBr) : 2208, 1664, 1587 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.40(6H, d, $J=6.64$ Hz), 5.33(1H, 7-plet, $J=6.64$ Hz), 6.87(1H, d, $J=9.57$ Hz), 7.01-7.14(2H, m), 7.28(1H, d, $J=9.57$ Hz), 7.51-7.61(2H, m)

APCI/MS: 257 $[\text{M}+\text{H}]^+$, 215

Elemental Analysis for $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}$

Calcd.: C, 70.30; H, 5.11; N, 10.93

Found : C, 70.33; H, 5.34; N, 11.05

Preparation 9

To a mixture of sulfuric acid (6 ml) and acetic acid (15 ml) was added 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone (3.00 g) and the mixture was heated at 100-105°C for 40 minutes. The solution was poured into a mixture of ice (90 g) and sodium carbonate (25.4 g), extracted with ethyl acetate (24 ml x 2), dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 3:7 v/v) to give 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone as a solid (451 mg).

mp: 67-68°C (n-hexane)

IR (KBr) : 1689, 1660, 1596 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.32(6H, d, $J=6.62$ Hz), 4.28(2H, s), 5.29(1H, 7-plet, $J=6.62$ Hz), 6.89(1H, d, $J=9.50$ Hz), 7.11-7.23(3H, m),

8.04-8.13(2H, m)

APCI/MS: 275 [M+H]⁺, 233

Elemental Analysis for C₁₅H₁₅FN₂O₂

Calcd.: C, 65.68; H, 5.51; N, 10.21

5 Found : C, 65.72; H, 5.65; N, 10.21

Preparation 10

In the presence of dichlorobis(triphenylphosphine)-
palladium(II) (1.47 g) and copper(I) iodide (1.47 g),
triethylamine (14.67 ml) was added dropwise to a mixture of
10 1-isopropyl-6-oxo- 1,6-dihydro-3-pyridazinyl
trifluoromethanesulfonate (20.10 g),
(trimethylsilyl)acetylene (24.81 ml) in tetrahydrofuran (300
ml) under ice-cooling for 2 hours. The mixture was stirred
at ambient temperature for 3 hours. The reaction mixture was
15 poured into a mixture of water and ethyl acetate. An organic
layer was washed with brine, dried over magnesium sulfate,
and concentrated under reduced pressure to give a residue.
The residue was purified by column chromatography on silica
gel (n-Hexane-EtOAc, 9:1 v/v) to give
20 2-isopropyl-6-[(trimethylsilyl)ethynyl]-3(2H)- pyridazinone
as a solid (16.10 g).

mp: 61-62.5°C (n-hexane)

IR (KBr) : 2160, 1664, 1587 cm⁻¹

¹H NMR (CDCl₃, δ) : 0.27(9H, s), 1.37(6H, d, J=6.64 Hz), 5.29(1H,
25 7-plet, J=6.64 Hz), 6.81(1H, d, J=9.54 Hz), 7.21(1H, d, J=9.54
Hz), 7.51-7.61(2H, m)

ESI/MS: 491 [2M+Na]⁺, 257 [M+Na]⁺, 235 [M+H]⁺

Elemental Analysis for C₁₂H₁₈N₂OSi

Calcd.: C, 61.50; H, 7.74; N, 11.95

30 Found : C, 61.25; H, 7.82; N, 12.00

Preparation 11

To a solution of 2-isopropyl-6-[(trimethylsilyl)ethynyl]-
3(2H)-pyridazinone and benzyltriethylammonium chloride (0.52

g) in a mixture of tetrahydrofuran (45 ml) and acetonitrile (45 ml) was added dropwise 12 N aqueous sodium hydroxide (60 ml) under ice-cooling. After stirring for 30 minutes, the mixture was acidified with concentrated hydrochloric acid under ice-cooling, extracted with chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 8:2 v/v) to give 6-ethynyl-2-isopropyl-3(2H)-pyridazinone as a solid (10.42 g).

mp: 103-104°C (acetone - n-hexane)

IR (KBr) : 3194, 2108, 1655, 1587 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.38 (6H, d, $J=6.64$ Hz), 3.19 (1H, s), 5.31 (1H, 7-plet, $J=6.64$ Hz), 6.85 (1H, d, $J=9.52$ Hz), 7.22 (1H, d, $J=9.52$ Hz)

ESI/MS: 185 $[\text{M}+\text{Na}]^+$, 163 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_9\text{H}_{10}\text{N}_2\text{O}$

Calcd.: C, 66.65; H, 6.21; N, 17.27

Found : C, 66.92; H, 6.28; N, 17.36

20 Preparation 12

In the presence of dichlorobis(triphenylphosphine)-palladium(II) (0.42 g) and copper(I) iodide (0.42 g), triethylamine (3.9 ml) was added dropwise to a mixture of 6-ethynyl-2-isopropyl-3(2H)-pyridazinone (3.25 g), 1-fluoro-4-iodobenzene (6.67 g) in dioxane (60 ml) at 75-80°C for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, a mixture of water and ethyl acetate was added to the reaction mixture. An organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-Hexane-EtOAc, 7:3 v/v) to give 6-[(4-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone as a solid (3.81 g).

mp: 105.5-106.5°C (n-hexane)

IR (KBr) : 2208, 1664, 1587 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.40(6H, d, $J=6.64$ Hz), 5.33(1H, 7-plet, $J=6.64$ Hz), 6.87(1H, d, $J=9.57$ Hz), 7.01-7.14(2H, m), 7.28(1H, d, $J=9.57$ Hz), 7.51-7.61(2H, m)

APCI/MS: 257 $[\text{M}+\text{H}]^+$, 215

Elemental Analysis for $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}$

Calcd.: C, 70.30; H, 5.11; N, 10.93

Found : C, 70.33; H, 5.34; N, 11.05

10 Preparation 13

To a mixture of 3-methoxy-6-iodopyridazine (30.0 g), 2-bromo-1-ethynylbenzene (34.5 g), dichlorobis(triphenylphosphine)palladium (II) (892 mg) and copper (I) iodide (242 mg) in DMF (150 ml) was added triethylamine (23.0 ml) at ambient temperature under N_2 atmosphere and the resultant mixture was allowed to stir at the same temperature for 13 hours. The reaction mixture was poured into water and extracted with ethyl acetate (x2). The combined extracts were washed with brine and water, dried over MgSO_4 and concentrated under reduced pressure. The crude material was purified by column chromatography (SiO_2 , n-Hexane-EtOAc, 10:1) to afford 3-[(2-bromophenyl)ethynyl]-6-methoxypyridazine.

mp: 99-100°C

IR (Nujol): 1699, 1651, 1558, 1540 cm^{-1}

25 NMR(CDCl_3 , δ): 4.18(3H, s), 6.97(1H, d, $J=9.2$ Hz), 7.24-7.37(2H, m), 7.56-7.67(3H, m)

ESI/MS: 311, 313 $[\text{M}+\text{Na}]^+$, APCI/MS: 289, 291 $[\text{M}+\text{H}]^+$

Preparation 14

1-(2-Bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was obtained from 3-[(2-bromophenyl)ethynyl]-6-methoxypyridazine according to a similar manner to that of Preparation 2.

IR (Neat): 2956, 2925, 1733, 1699, 1651 cm^{-1}

ESI/MS: 380, 382 [M+Na]⁺

Preparation 15

To a solution of 3-methoxy-6-methylpyridazine (371 mg) and ethyl 2-bromobenzoate (753 mg) in THF (4 ml) was added
5 dropwise 1M lithium bis(trimethylsilyl)amide in THF (5.98 ml) at 5°C over a period of 20 minutes under N₂ atmosphere and the resulting solution was stirred at the same temperature for 30 minutes. The reaction mixture was poured into ice/water and pH was adjusted to neutral with 1N HCl, and the mixture
10 was extracted with EtOAc (x2). The combined extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure to give 935 mg of yellow oil. The crude material was purified by silica-gel column chromatography (n-Hexane-EtOAc, 10:3) to afford
15 1-(2-bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone as yellow oil.

Preparation 16

4-(Bromophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was obtained from 1-(2-bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar
20 manner to that of Preparation 3.

mp: 180-181°C (EtOH)

IR (Nujol): 1649, 1637, 1576, 1560, 1538 cm⁻¹

NMR (DMSO-d₆, δ): 3.98(3H, s), 7.02(1H, d, J=9.1 Hz), 7.08(1H, d, J=9.1 Hz), 7.16(2H, brd. s), 7.30-7.45(3H, m), 7.58(1H, d, J=7.9 Hz), 8.65(1H, s)
25

ESI/MS: 380, 382 [M+Na]⁺

Preparation 17

In the presence of
30 dichlorobis(triphenylphosphine)palladium (II) (0.49 g) and copper(I) iodide (0.133 g), a solution of triethylamine (11.7 ml) in dioxane (10 ml) was added dropwise to a mixture of 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl-

trifluoromethanesulfonate (20.00 g) and ethynylbenzene (8.56 g) in dioxane (70 ml) at 75-80°C for 0.5 hour. The mixture was stirred at 75-80°C for 1.5 hours. After cooling, water and chloroform were added to the reaction mixture. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 85 : 15 v/v) to give 2-isopropyl-6-(phenylethynyl)-3(2H)-pyridazinone as a solid (16.17 g).

mp: 75.5-77°C (heptane)

IR (KBr) : 2218, 1669, 1583 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.40(6H, d, $J=6.65$ Hz), 5.33(1H, 7-plet, $J=6.65$ Hz), 6.87(1H, d, $J=9.57$ Hz), 7.26-7.42(4H, m),

7.52-7.60(2H, m)

ESI/MS: 499 $[\text{2M}+\text{Na}]^+$, 261 $[\text{M}+\text{Na}]^+$, 239 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}$

Calcd.: C, 75.61; H, 5.92; N, 11.76

Found : C, 75.79; H, 5.88; N, 11.74

Preparation 18

To a mixture of sulfuric acid (1 ml) and acetic acid (3 ml) was added 2-isopropyl-6-(phenylethynyl)-3(2H)-pyridazinone (479 mg) and the mixture was heated at 100-105°C for 2 hours. The solution was poured into water (80 ml), extracted with ethyl acetate (30 ml x 3), dried over magnesium sulfate, and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 25 : 75 v/v) to give 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone as a solid (451 mg).

mp: 50-53°C (diisopropyl ether - hexane)

IR (KBr): 1687, 1660, 1595 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.32(6H, d, $J=6.66$ Hz), 4.32(2H, s), 5.29(1H,

7-plet, $J=6.66$ Hz), 6.88 (1H, d, $J=9.50$ Hz), 7.18 (1H, d, $J=9.50$ Hz), 7.45-7.62 (3H, m), 8.01-8.07 (2H, m)

ESI/MS: 535 $[2M+Na]^+$, 279 $[M+Na]^+$, 257 $[M+H]^+$

Elemental Analysis for $C_{15}H_{16}N_2O_2$

5 Calcd.: C, 70.29; H, 6.29; N, 10.93

Found : C, 69.17; H, 6.32; N, 10.74

Preparation 19

To a mixture of 2-isopropyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone (500 mg) and N,N-dimethylformamide dimethyl acetal (0.518 ml) was heated at 100-105°C for one hour. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (chloroform) to give

6-[1-benzoyl-2-(dimethylamino)ethenyl]-2-isopropyl-3(2H)-pyridazinone as a solid (604 mg).

mp: 103-104.5°C (diisopropyl ether)

IR (KBr): 1647, 1628, 1583, 1554 cm^{-1}

1H NMR ($CDCl_3$, δ): 1.32 (6H, d, $J=6.64$ Hz), 2.89 (6H, s), 5.33 (1H, 7-plet, $J=6.64$ Hz), 6.75 (1H, d, $J=9.43$ Hz), 7.11 (1H, d, $J=9.43$ Hz), 7.26-7.48 (6H, m)

ESI/MS: 645 $[2M+Na]^+$, 334 $[M+Na]^+$, 312 $[M+H]^+$

Elemental Analysis for $C_{18}H_{21}N_3O_2 \cdot 0.1H_2O$

Calcd.: C, 69.03; H, 6.82; N, 13.42

Found : C, 69.08; H, 6.75; N, 13.34

25 Preparation 20

Under ice-cooling, potassium t-butoxide (1.75 g) was added to a suspension of 6-[1-benzoyl-2-(dimethylamino)ethenyl]-2-isopropyl-3(2H)-pyridazinone (1.21 g) and S-methylthiouronium sulfate (2.17 g) in methanol (15 ml). The mixture was stirred for one hour under ice-cooling and at ambient temperature for 30 hours. After removal of methanol under reduced pressure, a mixture of chloroform and water was added to a reaction mixture.

An organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (hexane - ethyl acetate 70 : 30 v/v) to give 2-isopropyl-6-[2-(methylthio)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone as a solid (943 mg).

mp: 143-144.5°C (ethanol - diisopropyl ether)

IR (KBr): 1655, 1593 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.33 (6H, d, $J=6.62$ Hz), 2.66 (3H, s), 5.33 (1H, 7-plet, $J=6.62$ Hz), 6.71 (1H, d, $J=9.70$ Hz), 6.75 (1H, d, $J=9.70$ Hz), 7.34-7.52 (5H, m), 8.73 (1H, s)

ESI/MS: 699 $[\text{2M}+\text{Na}]^+$, 361 $[\text{M}+\text{Na}]^+$, 399 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{18}\text{H}_{18}\text{N}_4\text{OS}$

Calcd.: C, 63.88; H, 5.36; N, 16.56

Found : C, 64.00; H, 5.24; N, 16.57

15 Preparation 21

A mixture of 2-isopropyl-6-[2-(methylthio)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone (990 mg) and urea-hydrogen peroxide complex (550 mg) in acetic acid (0.99 ml) was stirred at ambient temperature for 40 hours. After addition of chloroform, the mixture was washed with water, aqueous sodium hydrogen carbonate solution and brine, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol- chloroform 3:97 v/v) to give 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone as a solid (516 mg).

mp: 178-179°C (acetone - diisopropyl ether)

IR (KBr): 1666, 1591 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.35 (6H, d, $J=6.66$ Hz), 3.06 (3H, s), 5.35 (1H, 7-plet, $J=6.66$ Hz), 6.77 (1H, d, $J=9.56$ Hz), 6.84 (1H, d, $J=9.56$ Hz), 7.38-7.57 (5H, m), 9.06 (1H, s)

ESI/MS: 731 $[\text{2M}+\text{Na}]^+$, 377 $[\text{M}+\text{Na}]^+$

Elemental Analysis for $C_{18}H_{18}N_4O_2S$

Calcd.: C, 61.00; H, 5.12; N, 15.81

Found : C, 61.12; H, 5.16; N, 15.56

Preparation 22

- 5 6-[(2-Fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was obtained from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-fluoro-2-iodobenzene according to a similar manner to that of Preparation 12.

mp: 84.5-86°C (diisopropyl ether - hexane)

- 10 IR (KBr): 2224, 1660, 1644, 1583 cm^{-1}

1H NMR ($CDCl_3$, δ): 1.41(6H, d, $J=6.62$ Hz), 5.34(1H, 7-plet, $J=6.62$ Hz), 6.88(1H, d, $J=9.52$ Hz), 7.12-7.20(2H, m), 7.32(1H, d, $J=9.52$ Hz), 7.33-7.41(1H, m), 7.52-7.60(1H, m)

ESI/MS: 535 $[2M+Na]^+$, 279 $[M+Na]^+$, 257 $[M+H]^+$

- 15 Elemental Analysis for $C_{15}H_{13}FN_2O$

Calcd.: C, 70.30; H, 5.11; N, 10.93

Found : C, 70.38; H, 5.14; N, 10.95

Preparation 23

- 20 6-[2-(2-Fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[(2-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

IR (Neat): 1685, 1664, 1593 cm^{-1}

- 25 1H NMR ($CDCl_3$, δ): 1.32(6H, d, $J=6.65$ Hz), 4.28(2H, s), 5.29(1H, 7-plet, $J=6.65$ Hz), 6.89(1H, d, $J=9.50$ Hz), 7.17(1H, d, $J=9.50$ Hz), 7.40-7.49(1H, m), 7.55-7.62(1H, m), 7.89-7.95(1H, m), 8.02-8.04(1H, m)

ESI/MS: 571 $[2M+Na]^+$, 297 $[M+Na]^+$, 275 $[M+H]^+$

Preparation 24

- 30 6-[2-(Dimethylamino)-1-(2-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(2-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar

manner to that of Example 13(1).

mp: 79.5-81.5°C (chloroform - hexane)

IR (KBr): 1668, 1591 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.28 (6H, d, $J=6.62$ Hz), 2.89 (6H, br.s), 5.29 (1H, 7-plet, $J=6.62$ Hz), 6.77 (1H, d, $J=9.46$ Hz), 6.95-7.39 (6H, m)
ESI/MS: 681 $[\text{2M}+\text{Na}]^+$, 352 $[\text{M}+\text{Na}]^+$, 330 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{18}\text{H}_{20}\text{FN}_3\text{O}_2$

Calcd.: C, 65.64; H, 6.12; N, 12.76

Found : C, 65.49; H, 6.36; N, 12.80

10 Preparation 25

6-[(3-Fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-fluoro-3-iodobenzene according to a similar manner to that of Preparation 12.

15 mp: 95.5-96.5°C (acetone - hexane)

IR (KBr): 2220, 1660, 1606, 1585 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.41 (6H, d, $J=6.62$ Hz), 5.34 (1H, 7-plet, $J=6.62$ Hz), 6.88 (1H, d, $J=9.52$ Hz), 7.12-7.20 (2H, m), 7.32 (1H, d, $J=9.52$ Hz), 7.33-7.41 (1H, m), 7.52-7.60 (1H, m)

20 ESI/MS: 535 $[\text{2M}+\text{Na}]^+$, 279 $[\text{M}+\text{Na}]^+$, 257 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{15}\text{H}_{13}\text{FN}_2\text{O}$

Calcd.: C, 70.30; H, 5.11; N, 10.93

Found : C, 70.22; H, 5.16; N, 10.94

Preparation 26

25 6-[2-(3-Fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[(3-fluorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 80-81°C (diisopropyl ether - hexane)

30 IR (KBr): 1680, 1658, 1591 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.32 (6H, d, $J=6.60$ Hz), 4.29 (2H, s), 5.29 (1H, 7-plet, $J=6.60$ Hz), 6.89 (1H, d, $J=9.48$ Hz), 7.18 (1H, d, $J=9.48$

Hz), 7.26-7.33(1H, m), 7.43-7.53(1H, m), 7.70-7.77(1H, m),
7.80-7.86(1H, m)

ESI/MS: 274 [2M+Na]⁺, 297 [M+Na]⁺, 275 [M+H]⁺

Elemental Analysis for C₁₅H₁₅FN₂O₂

5 Calcd.: C, 65.68; H, 5.51; N, 10.21

Found : C, 65.73; H, 5.61; N, 10.24

Preparation 27

6-[2-(Dimethylamino)-1-(3-fluorobenzoyl)ethenyl]-2-
isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(3-
10 fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and
N-(dimethoxymethyl)-N,N-dimethylamine according to a similar
manner to that of Example 13(1).

IR (Neat): 1651, 1574, 1558 cm⁻¹

¹H NMR (CDCl₃, δ): 1.32(6H, d, J=6.63 Hz), 2.89(6H, br.s), 5.33(1H,
15 7-plet, J=6.63 Hz), 6.75(1H, d, J=9.46 Hz), 7.07-7.36(5H, m),
7.45(1H, s)

ESI/MS: 681 [2M+Na]⁺, 352 [M+Na]⁺, 330 [M+H]⁺

Preparation 28

6-[(2-Chlorophenyl)ethynyl]-2-isopropyl-3(2H)-
20 pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-
pyridazinone and 1-chloro-2-iodobenzene according to a similar
manner to that of Preparation 12.

mp: 95.5-96°C (acetone - hexane)

IR (KBr): 1660, 1585 cm⁻¹

25 ¹H NMR (CDCl₃, δ): 1.41(6H, d, J=6.63 Hz), 5.34(1H, 7-plet,
J=6.63 Hz), 6.88(1H, d, J=9.56 Hz), 7.24-7.37(3H, m),
7.43-7.47(1H, m), 7.58-7.64(1H, m)

ESI/MS: 569 and 567 [2M+Na]⁺, 297 and 295 [M+Na]⁺

Elemental Analysis for C₁₅H₁₃ClN₂O

30 Calcd.: C, 66.06; H, 4.80; N, 10.27

Found : C, 66.17; H, 4.80; N, 10.26

Preparation 29

6-[2-(2-Chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-

pyridazinone was prepared from 6-[(2-chlorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 81.5-82°C (diisopropyl ether - hexane)

5 IR (KBr): 1685, 1657, 1589 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.27(6H, d, $J=6.66$ Hz), 4.03(2H, s), 5.26(1H, 7-plet, $J=6.66$ Hz), 6.89(1H, d, $J=9.48$ Hz), 7.19(1H, d, $J=9.48$ Hz), 7.29-7.46(3H, m), 7.55-7.60(1H, m)

ESI/MS: 605 and 603 $[2\text{M}+\text{Na}]^+$, 315 and 313 $[\text{M}+\text{Na}]^+$,

10 293 and 291 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{15}\text{H}_{15}\text{ClN}_2\text{O}_2$

Calcd.: C, 61.94; H, 5.20; N, 9.63

Found : C, 61.54; H, 5.35; N, 9.54

Preparation 30

15 6-[2-(Dimethylamino)-1-(2-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(2-chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

20 IR (Neat): 1655, 1576 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.32(6H, d, $J=6.64$ Hz), 2.89(6H, br.s), 5.31(1H, 7-plet, $J=6.64$ Hz), 6.76(1H, d, $J=9.44$ Hz), 7.21-7.36(6H, m)

ESI/MS: 681 $[2\text{M}+\text{Na}]^+$, 352 $[\text{M}+\text{Na}]^+$, 330 $[\text{M}+\text{H}]^+$

Preparation 31

25 6-[(3-Chlorophenyl)ethynyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl trifluoromethanesulfonate and 1-chloro-3-ethynylbenzene according to a similar manner to that of Preparation 8.

30 mp: 94-95°C (heptane)

IR (KBr): 1664, 1589 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.40(6H, d, $J=6.65$ Hz), 5.33(1H, 7-plet,

J=6.65 Hz), 6.88(1H, d, J=9.54 Hz), 7.25-7.48(4H, m),
7.55-7.58(1H, m)

ESI/MS: 569 and 567 [2M+Na]⁺, 297 and 295 [M+Na]⁺,
275 and 273 [M+H]⁺

5 Elemental Analysis for C₁₅H₁₃ClN₂O

Calcd.: C, 66.06; H, 4.80; N, 10.27

Found : C, 66.10; H, 4.83; N, 10.27

Preparation 32

6-[2-(3-Chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-
10 pyridazinone was prepared from 6-[(3-chlorophenyl)ethynyl]-2-
isopropyl-3(2H)-pyridazinone according to a similar manner
to that of Preparation 9.

mp: 85-86°C (diisopropyl ether - hexane)

IR (KBr): 1676, 1658, 1591 cm⁻¹

15 ¹H NMR (CDCl₃, δ): 1.32(6H, d, J=6.65 Hz), 4.28(2H, s), 5.29(1H,
7-plet, J=6.65 Hz), 6.89(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50
Hz), 7.40-7.49(1H, m), 7.55-7.62(1H, m), 7.89-7.95(1H, m),
8.02-8.04(1H, m)

ESI/MS: 605 and 603 [2M+Na]⁺, 315 and 313 [M+Na]⁺,

20 293 and 291 [M+H]⁺

Elemental Analysis for C₁₅H₁₅ClN₂O₂

Calcd.: C, 61.97; H, 5.20; N, 9.63

Found : C, 62.10; H, 5.25; N, 9.68

Preparation 33

25 6-[2-(Dimethylamino)-1-(3-chlorobenzoyl)ethenyl]-2-
isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(3-
chlorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone and
N-(dimethoxymethyl)-N,N-dimethylamine according to a similar
manner to that of Example 13(1).

30 IR (Neat): 1657, 1579, 1556 cm⁻¹

¹H NMR (CDCl₃, δ): 1.32(6H, d, J=6.66 Hz), 2.90(6H, br.s), 5.34(1H,
7-plet, J=6.66 Hz), 6.76(1H, d, J=9.40 Hz), 7.08(1H, d, J=9.40
Hz), 7.21-7.38(4H, m), 7.44(1H, s)

ESI/MS: 348 and 346 $[M+H]^+$

Elemental Analysis for $C_{18}H_{20}ClN_3O_2 \cdot 0.4H_2O$

Calcd.: C, 61.24; H, 5.94; N, 11.90

Found : C, 61.20; H, 6.06; N, 11.78

5 Preparation 34

2-Isopropyl-6-([2-(trifluoromethyl)phenyl]ethynyl)-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-iodo-2-(trifluoromethyl)benzene according to a similar manner to that of Preparation 12.

10 mp: 88.5-90°C (hexane)

IR (KBr): 1664, 1591 cm^{-1}

1H NMR ($CDCl_3$, δ): 1.41(6H, d, $J=6.60$ Hz), 5.34(1H, 7-plet, $J=6.60$ Hz), 6.89(1H, d, $J=9.54$ Hz), 7.30(1H, d, $J=9.54$ Hz), 7.45-7.60(2H, m), 7.69-7.76(2H, m)

15 ESI/MS: 635 $[2M+Na]^+$, 329 $[M+Na]^+$, 307 $[M+H]^+$

Elemental Analysis for $C_{16}H_{13}F_3N_2O$

Calcd.: C, 62.74; H, 4.28; N, 9.15

Found : C, 62.82; H, 4.36; N, 9.14

Preparation 35

20 2-Isopropyl-6-([2-oxo-2-([2-(trifluoromethyl)phenyl]ethyl)-3(2H)-pyridazinone was prepared from 2-isopropyl-6-([2-(trifluoromethyl)phenyl]ethynyl)-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

mp: 91-92.5°C (diisopropyl ether - hexane)

25 IR (KBr): 1709, 1654, 1586 cm^{-1}

1H NMR ($CDCl_3$, δ): 1.29(6H, d, $J=6.68$ Hz), 4.18(2H, s), 5.28(1H, 7-plet, $J=6.68$ Hz), 6.89(1H, d, $J=9.50$ Hz), 7.17(1H, d, $J=9.50$ Hz), 7.50-7.79(4H, m)

ESI/MS: 671 $[2M+Na]^+$, 347 $[M+Na]^+$, 325 $[M+H]^+$

30 Elemental Analysis for $C_{16}H_{15}F_3N_2O_2$

Calcd.: C, 59.26; H, 4.66; N, 8.64

Found : C, 59.39; H, 4.69; N, 8.63

Preparation 36

6-(2-(Dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl)-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{2-oxo-2-[2-(trifluoromethyl)phenyl]-ethyl}-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (KBr): 1654, 1587 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.33(6H, d, $J=6.65$ Hz), 2.84(6H, br.s), 5.33(1H, 7-plet, $J=6.65$ Hz), 6.79(1H, d, $J=8.96$ Hz), 7.21-7.70(6H, m)

ESI/MS: 781 $[2\text{M}+\text{Na}]^+$, 402 $[\text{M}+\text{Na}]^+$, 380 $[\text{M}+\text{H}]^+$

Preparation 37

2-Isopropyl-6-([3-(trifluoromethyl)phenyl]ethynyl)-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-iodo-3-(trifluoromethyl)benzene according to a similar manner to that of Preparation 12.

mp: 102.5-104°C (hexane)

IR (KBr): 1662, 1589 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.41(6H, d, $J=6.60$ Hz), 5.34(1H, 7-plet, $J=6.60$ Hz), 6.89(1H, d, $J=9.54$ Hz), 7.30(1H, d, $J=9.54$ Hz), 7.47-7.56(1H, m), 7.65(1H, d, $J=7.86$ Hz), 7.74(1H, d, $J=7.86$ Hz), 7.84(1H, s)

ESI/MS: 635 $[2\text{M}+\text{Na}]^+$, 329 $[\text{M}+\text{Na}]^+$

Elemental Analysis for $\text{C}_{16}\text{H}_{13}\text{F}_3\text{N}_2\text{O}$

Calcd.: C, 62.74; H, 4.28; N, 9.15

Found : C, 62.72; H, 4.29; N, 9.19

Preparation 38

2-Isopropyl-6-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-6-([3-(trifluoromethyl)phenyl]ethynyl)-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

IR (Neat): 1695, 1657, 1591 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.31(6H, d, $J=6.62$ Hz), 4.34(2H, s), 5.28(1H,

7-plet, $J=6.62$ Hz), 6.90 (1H, d, $J=9.50$ Hz), 7.18 (1H, d, $J=9.50$ Hz), 7.66 (1H, t, $J=7.80$ Hz), 7.87 (1H, d, $J=7.90$ Hz), 8.23 (1H, d, $J=7.90$ Hz), 8.30 (1H, s)

ESI/MS: 671 $[2M+Na]^+$, 347 $[M+Na]^+$, 325 $[M+H]^+$

5 Elemental Analysis for $C_{16}H_{15}F_3N_2O_2$

Calcd.: C, 59.26; H, 4.66; N, 8.64

Found : C, 58.99; H, 4.75; N, 8.57

Preparation 39

10 6-{3-(Dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{2-oxo-2-[3-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

IR (Neat): 1651, 1558 cm^{-1}

15 1H NMR ($CDCl_3$, δ): 1.33 (6H, d, $J=6.66$ Hz), 2.92 (6H, br.s), 5.32 (1H, $J=6.66$ Hz), 6.76 (1H, d, $J=9.40$ Hz), 7.07 (1H, d, $J=9.40$ Hz), 7.41-7.68 (5H, m)

ESI/MS: 781 $[2M+Na]^+$, 402 $[M+Na]^+$, 380 $[M+H]^+$

Preparation 40

20 2-Isopropyl-6-{[4-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone was prepared from 6-ethynyl-2-isopropyl-3(2H)-pyridazinone and 1-iodo-4-(trifluoromethyl)benzene according to a similar manner to that of Preparation 12.

mp: 48-50°C (hexane)

25 IR (KBr) : 1662, 1585 cm^{-1}

1H NMR ($CDCl_3$, δ): 1.41 (6H, d, $J=6.60$ Hz), 5.34 (1H, 7-plet, $J=6.60$ Hz), 6.89 (1H, d, $J=9.54$ Hz), 7.30 (1H, d, $J=9.54$ Hz), 7.64 (1H, d, $J=8.88$ Hz), 7.68 (1H, d, $J=8.88$ Hz)

ESI/MS: 635 $[2M+Na]^+$, 329 $[M+Na]^+$, 307 $[M+H]^+$

30 Elemental Analysis for $C_{16}H_{13}F_3N_2O$

Calcd.: C, 62.74; H, 4.28; N, 9.15

Found : C, 62.91; H, 4.47; N, 9.06

Preparation 41

2-Isopropyl-6-{2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{[4-(trifluoromethyl)phenyl]ethynyl}-3(2H)-pyridazinone according to a similar manner to that of Preparation 9.

5 mp: 99-101°C (hexane)

IR (KBr): 1686, 1660, 1595 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.31 (6H, d, $J=6.62$ Hz), 4.34 (2H, s), 5.28 (1H, 7-plet, $J=6.62$ Hz), 6.90 (1H, d, $J=9.50$ Hz), 7.18 (1H, d, $J=9.50$ Hz), 7.77 (2H, d, $J=8.15$ Hz), 8.15 (2H, d, $J=8.15$ Hz)

10 ESI/MS: 671 $[2\text{M}+\text{Na}]^+$, 347 $[\text{M}+\text{Na}]^+$, 325 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{16}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_2$

Calcd.: C, 59.26; H, 4.66; N, 8.64

Found : C, 59.45; H, 4.66; N, 8.70

Preparation 42

15 6-{4-(Dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 2-isopropyl-6-{2-oxo-2-[4-(trifluoromethyl)phenyl]ethyl}-3(2H)-pyridazinone and N-(dimethoxymethyl)-N,N-dimethylamine according to a similar manner to that of Example 13(1).

20

IR (Neat): 1651, 1558 cm^{-1}

^1H NMR (CDCl_3 , δ): 1.29 (6H, d, $J=6.64$ Hz), 2.91 (6H, br.s), 5.32 (1H, 7-plet, $J=6.64$ Hz), 6.79 (1H, d, $J=9.48$ Hz), 7.12 (1H, d, $J=9.48$ Hz), 7.41 (1H, s), 7.51-7.63 (4H, m)

25 ESI/MS: 781 $[2\text{M}+\text{Na}]^+$, 402 $[\text{M}+\text{Na}]^+$, 380 $[\text{M}+\text{H}]^+$

Preparation 43

30 4'-Methoxyacetophenone (1.5 g) was dissolved in tetrahydrofuran (25 ml). To the solution was added sodium tert-butoxide (575 mg) at 25°C. To the solution was added tris(dibenzylideneacetone)-dipalladium(0) (229 mg) and racemic-2,2'-bis(diphenyl phosphino)-1,1'-binaphthyl (311 mg), followed by 3-methoxy-6-chloropyridazine (720 mg). The mixture was heated at 75°C and stirred for 3 hours.

The reaction mixture was portioned to dichloromethane and 0.1N-hydrochloric acid. The organic layer was separated. The aqueous layer was extracted with dichloromethane. The combined organic layer was dried over magnesium sulfate. The solution
5 was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (ethyl acetate: hexane=1:1) to give 1-(4-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone (671 mg).

IR (KBr): 3490, 1668, 1469, 1263 cm^{-1}

10 NMR (DMSO- d_6 , δ): 3.86(3H, s), 4.00(3H, s), 4.63(2H, s), 7.06(2H, d, $J=9.8$ Hz), 7.20(1H, d, $J=9.2$ Hz), 7.56(1H, d, $J=9.2$ Hz), 8.05(1H, d, $J=9.8$ Hz)

ESI/MS: 259 $[\text{M}+\text{H}]^+$, 281 $[\text{M}+\text{Na}]^+$

Preparation 44

15 1-(3-Fluorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-fluoroacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3488, 1670, 1469, 1260 cm^{-1}

20 NMR (DMSO- d_6 , δ): 3.99(3H, s), 4.72 (2H, s), 7.19-7.94 (6H, m)

ESI/MS: 247 $[\text{M}+\text{H}]^+$, 269 $[\text{M}+\text{Na}]^+$

Preparation 45

25 1-(3-Fluoro-4-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)-ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-fluoro-4'-methoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3480, 1685, 1444, 1230 cm^{-1}

30 NMR (DMSO- d_6 , δ): 3.95(3H, s), 4.00(3H, s), 4.65(2H, s), 7.20(1H, d, $J=9.0$ Hz), 7.29-7.38(1H, m), 7.67(1H, d, $J=9.0$ Hz), 7.83-7.98(2H, m)

ESI/MS: 277 $[\text{M}+\text{H}]^+$, 299 $[\text{M}+\text{Na}]^+$

Preparation 46

1-(4-Chlorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 4'-chloroacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3485, 1675, 1470, 1265 cm^{-1}

NMR (DMSO- d_6 , δ): 4.00(3H, s), 4.70(2H, s), 7.19-8.10(6H, m)

ESI/MS: 263 and 265 $[\text{M}+\text{H}]^+$, 285 and 287 $[\text{M}+\text{Na}]^+$

Preparation 47

2-(6-Methoxy-3-pyridazinyl)-1-(3-pyridinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3-acetylpyridine according to a similar manner to that of Preparation 43.

IR (KBr): 3485, 1675, 1470, 1265 cm^{-1}

NMR (DMSO- d_6 , δ): 4.00(3H, s), 4.76(2H, s), 7.15-9.24(6H, m)

ESI/MS: 230 $[\text{M}+\text{H}]^+$, 252 $[\text{M}+\text{Na}]^+$

Preparation 48

2-(6-Methoxy-3-pyridazinyl)-1-(4-pyridinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 4-acetylpyridine according to a similar manner to that of Preparation 43.

IR (KBr): 3490, 1665, 1465, 1245 cm^{-1}

NMR (DMSO- d_6 , δ): 4.01(3H, s), 4.75(2H, s), 7.14-7.39(2H, m), 7.58-7.93(2H, m), 8.67-8.86(2H, m)

ESI/MS: 230 $[\text{M}+\text{H}]^+$

Preparation 49

2-(6-Methoxy-3-pyridazinyl)-1-(1,3-thiazol-2-yl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2-acetylthiazole according to a similar manner to that of Preparation 43.

IR (KBr): 3485, 1675, 1470, 1265 cm^{-1}

NMR (DMSO- d_6 , δ): 3.93(3H, s), 4.76(2H, s), 7.20-8.50(4H, m)

ESI/MS: 236 [M+H]⁺, 258 [M+Na]⁺

Preparation 50

1-(2-Furyl)-2-(6-methoxy-3-pyridazinyl)ethanone was
5 prepared from 3-methoxy-6-chloropyridazine and 2-acetylfuran
according to a similar manner to that of Preparation 43.

IR (KBr): 3490, 1675, 1460, 1265 cm^{-1}

NMR (CDCl_3 , δ): 4.11(3H, s), 4.45(2H, s), 6.55-6.58(1H, m),
6.96(1H, d, $J=7.0$ Hz), 7.26(1H, s), 7.37-7.39(1H, m), 7.44(1H,
10 d, $J=7.0$ Hz), 7.63(1H, s)

ESI/MS: 219 [M+H]⁺, 241 [M+Na]⁺

Preparation 51

2-(6-Methoxy-3-pyridazinyl)-1-(4-methylphenyl)ethanone
was prepared from 3-methoxy-6-chloropyridazine and
15 4'-methylacetophenone according to a similar manner to that
of Preparation 43.

IR (KBr): 3490, 1675, 1460, 1265 cm^{-1}

NMR (CDCl_3 , δ): 1.59(3H, s), 4.11(3H, s), 4.58(2H, s), 6.95(1H,
d, $J=9.0$ Hz), 7.27(2H, d, $J=6.6$ Hz), 7.42(1H, d, $J=9.0$ Hz),
20 8.00(2H, d, $J=6.6$ Hz)

ESI/MS: 243 [M+H]⁺, 265 [M+Na]⁺

Preparation 52

1-(3,4-Difluorophenyl)-2-(6-methoxy-3-pyridazinyl)-
ethanone was prepared from 3-methoxy-6-chloropyridazine and
25 3',4'-difluoroacetophenone according to a similar manner to
that of Preparation 43.

IR (KBr): 3485, 1685, 1600, 1465, 1260 cm^{-1}

NMR (DMSO- d_6 , δ): 4.03(3H, s), 4.55(2H, s), 6.91(1H, d, $J=9.6$
Hz), 7.18(1H, d, $J=9.6$ Hz), 7.63-7.97 (3H, m)

30 ESI/MS: 265 [M+H]⁺, 287 [M+Na]⁺

Preparation 53

1-(3,4-Dimethoxyphenyl)-2-(6-methoxy-3-pyridazinyl)-

ethanone was prepared from 3-methoxy-6-chloropyridazine and 3',4'-dimethoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3480, 1680, 1595, 1455, 1260 cm^{-1}

5 NMR (DMSO-d_6 , δ): 3.93(3H, s), 3.95(3H, s), 4.11(3H, s), 4.56(2H, s), 6.89-6.97(2H, m), 7.43(1H, d, $J=9.0$ Hz), 7.59(1H, d, $J=2.0$ Hz), 7.82(1H, dd, $J=8.2$, 2 Hz)

ESI/MS: 289 $[\text{M}+\text{H}]^+$, 311 $[\text{M}+\text{Na}]^+$

Preparation 54

10 1-(3,4-Dichlorophenyl)-2-(6-methoxy-3-pyridazinyl)-ethanone was prepared from 3-methoxy-6-chloropyridazine and 3',4'-dichloroacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3480, 1680, 1605, 1460, 1260 cm^{-1}

15 NMR (CDCl_3 , δ): 4.12(3H, s), 4.56(2H, s), 6.91-7.00(2H, m), 7.22-8.16(3H, m)

ESI/MS: 297, 299 and 301 $[\text{M}+\text{H}]^+$, 319, 321 and 323 $[\text{M}+\text{Na}]^+$

Preparation 55

20 2-(6-Methoxy-3-pyridazinyl)-1-(2-methylphenyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2'-methylacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3475, 1690, 1600, 1465, 1260 cm^{-1}

25 NMR (CDCl_3 , δ): 2.52(3H, s), 4.12(3H, s), 4.56(2H, s), 6.97(1H, d, $J=9.0$ Hz), 7.10-7.42(4H, m), 7.95(2H, d, $J=6.6$ Hz)

ESI/MS: 243 $[\text{M}+\text{H}]^+$, 265 $[\text{M}+\text{Na}]^+$

Preparation 56

30 1-(2-Methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2'-methoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3375, 1690, 1600, 1460, 1260 cm^{-1}

NMR (CDCl₃, δ): 3.91(3H, s), 4.11(3H, s), 4.64(2H, s), 6.95(1H, d, J=9.0 Hz), 7.02(2H, m), 7.39(1H, d, J=9.0 Hz), 7.46-7.94(1H, m), 7.76-7.81(1H, m)

ESI/MS: 259 [M+H]⁺, 281 [M+Na]⁺

5 Preparation 57

2-(6-Methoxy-3-pyridazinyl)-1-(2-thienyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 2-acetylthiophene according to a similar manner to that of Preparation 43.

10 IR (KBr): 3385, 1685, 1585, 1460, 1260 cm⁻¹

NMR (CDCl₃, δ): 4.11(3H, s), 4.53(2H, s), 6.90(1H, d, J=9.0 Hz) 7.13-7.17(1H, m), 7.68(1H, d, J=9.0 Hz), 7.69(1H, d, J=5.0 Hz), 7.97(1H, d, J=4.0 Hz)

ESI/MS: 235 [M+H]⁺, 257 [M+Na]⁺

15 Preparation 58

2-(6-Methoxy-3-pyridazinyl)-1-(3-methylphenyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-methylacetophenone according to a similar manner to that of Preparation 43.

20 IR (KBr): 3475, 1690, 1600, 1465, 1260 cm⁻¹

NMR (CDCl₃, δ): 2.42(3H, s), 4.12(3H, s), 4.61(2H, s), 6.96(1H, d, J=9.0 Hz), 7.10-7.45(4H, m), 7.90(2H, d, J=6.6 Hz)

ESI/MS: 243 [M+H]⁺, 265 [M+Na]⁺

Preparation 59

25 1-(3-Methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone was prepared from 3-methoxy-6-chloropyridazine and 3'-methoxyacetophenone according to a similar manner to that of Preparation 43.

IR (KBr): 3470, 1688, 1605, 1470, 1260 cm⁻¹

30 NMR (CDCl₃, δ): 3.89(3H, s), 4.21(3H, s), 4.61(2H, s), 6.96(1H, d, J=9.0 Hz), 7.02(2H, m), 7.42(1H, d, J=9.0 Hz), 7.46-7.94(1H, m), 7.76-7.81(1H, m)

ESI/MS: 259 [M+H]⁺, 281 [M+Na]⁺

Preparation 60

1-(4-Methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone
(516 mg) was dissolved in N,N-dimethyl formamide dimethylacetal
5 (10 ml). The solution was heated at 90°C for 2 hours. The solution
was cooled to ambient temperature. Evaporation of solvent in
vacuo gave oily black residue. The residue was dissolved in
ethanol (10 ml). To the solution was added guanidine hydrochloride
(384 mg) and 28% sodium methylate in methanol solution (0.77
10 ml). The reaction mixture was heated at 80-90°C, and stirred
for 2 hours. The mixture was cooled to ambient temperature, and
portioned to ethyl acetate and water. The organic layer was
separated and washed with brine. The combined aqueous layer
was extracted with ethyl acetate. The combined organic layer
15 was dried over magnesium sulfate. The solution was concentrated
under reduced pressure to give oily residue. The above residue
was purified by column chromatography on silica gel (chloroform:
methanol = 20:1) to give

4-(4-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-
20 pyrimidinamine, which was crystallized from ethanol-water (1:2
30 ml) (509 mg).

IR (KBr): 3376, 1610, 1533, 1463, 1251 cm⁻¹

NMR (DMSO-d₆, δ): 3.75 (3H, s), 4.03 (3H, s), 6.90 (1H, d, J=10
Hz), 6.99 (2H, brs), 7.02-7.13 (4H, m), 7.25 (1H, d), 8.43 (1H,
25 s)

ESI/MS: 310 [M+H]⁺, 332 [M+Na]⁺

Preparation 61

4-(3-Fluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-
pyrimidinamine was prepared from
30 1-(3-fluorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone
according to a similar manner to that of Preparation 60.

IR (KBr): 3322, 1654, 1575, 1444, 1297 cm⁻¹

NMR (DMSO-d₆, δ): 4.02 (3H, s), 6.99-7.45 (6H, m), 8.51 (1H, s)

ESI/MS: 298 [M+H]⁺, 320 [M+Na]⁺

Preparation 62

4-(3-Fluoro-4-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared from

5 1-(3-fluoro-4-methoxyphenyl)-

2-(6-methoxy-3-pyridazinyl)ethanone according to a similar
manner to that of Preparation 60.

IR(KBr): 3330, 1660, 1575, 1440, 1280 cm⁻¹

10 NMR (DMSO-d₆, δ): 3.83(3H, s), 4.04(3H, s), 6.94(1H, dd, J=1.16,
8.6 Hz), 7.05-7.26(6H, m), 8.45(1H, s)

ESI/MS: 328 [M+H]⁺, 350 [M+Na]⁺

Preparation 63

4-(4-Chlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-
pyrimidinamine was prepared from 1-(4-chlorophenyl)-2-(6-
15 methoxy-3-pyridazinyl)ethanone according to a similar manner
to that of Preparation 60.

IR (KBr): 3380, 1620, 1533, 1463, 1260 cm⁻¹

NMR (DMSO-d₆, δ): 4.03(3H, s), 7.06-7.44(6H, m), 8.49(1H, s)

ESI/MS: 314 and 316 [M+H]⁺, 336 and 338 [M+Na]⁺

20 Preparation 64

5-(6-Methoxy-3-pyridazinyl)-4-(3-pyridinyl)-2-
pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-
1-(3-pyridinyl)ethanone according to a similar manner to that
of Preparation 60.

25 IR (KBr): 3530, 1680, 1575, 1450, 1260 cm⁻¹

NMR (DMSO-d₆, δ): 4.02(3H, s), 7.11(1H, d, J=9.2 Hz), 7.16(2H,
brs), 7.32(1H, d, J=9.2 Hz), 7.36-7.40(1H, m), 7.64-7.70(1H,
m), 8.44-8.45(1H, m), 8.54(1H, s), 8.53-8.57(1H, m)

30 ESI/MS: 281 [M+H]⁺, 303 [M+Na]⁺

Preparation 65

5-(6-Methoxy-3-pyridazinyl)-4-(4-pyridinyl)-2-

pyrimidinamine was prepared from
2-(6-methoxy-3-pyridazinyl)-1-(4-pyridinyl)ethanone
according to a similar manner to that of Preparation 60.

IR (KBr): 3535, 1680, 1580, 1460, 1250 cm^{-1}

5 NMR (DMSO- d_6 , δ): 4.01 (3H, s), 7.12 (1H, d, $J=9.2$ Hz), 7.21-7.25 (4H, m), 7.32 (1H, d, $J=9.2$ Hz), 8.55 (1H, s), 8.53-8.57 (2H, m)

ESI/MS: 281 $[\text{M}+\text{H}]^+$, 303 $[\text{M}+\text{Na}]^+$

Preparation 66

10 5-(6-Methoxy-3-pyridazinyl)-4-(1,3-thiazol-2-yl)-2-pyrimidinamine was prepared from
2-(6-methoxy-3-pyridazinyl)-1-(1,3-thiazol-2-yl)ethanone
according to a similar manner to that of Preparation 60.

IR(KBr): 3540, 1620, 1580, 1455, 1255 cm^{-1}

15 NMR (DMSO- d_6 , δ): 4.06 (3H, s), 7.13 (1H, d, $J=9.2$ Hz), 7.21 (2H, s), 7.60 (1H, d, $J=9.2$ Hz), 7.77 (1H, d, $J=1.1$ Hz), 7.90 (1H, d, $J=1.1$ Hz), 8.43 (1H, s)

ESI/MS: 287 $[\text{M}+\text{H}]^+$, 309 $[\text{M}+\text{Na}]^+$

Preparation 67

20 4-(2-Furyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(2-furyl)-2-(6-methoxy-3-pyridazinyl)-ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3199, 1662, 1570, 1463, 1295 cm^{-1}

25 NMR (DMSO- d_6 , δ): 4.05 (3H, s), 6.55-6.58 (1H, m), 6.77 (1H, d, $J=3.6$ Hz), 7.01 (2H, s), 7.21 (1H, d, $J=9.2$ Hz), 7.49 (1H, d, $J=9.2$ Hz), 7.66-7.67 (1H, m), 8.33 (1H, s)

ESI/MS: 270 $[\text{M}+\text{H}]^+$, 292 $[\text{M}+\text{Na}]^+$

Preparation 68

30 5-(6-Methoxy-3-pyridazinyl)-4-(4-methylphenyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(4-methylphenyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3180, 1625, 1567, 1460, 1298 cm^{-1}

NMR (DMSO- d_6 , δ): 2.29(3H, s), 4.03(sH, s), 7.00-7.21(8H, m), 8.45(1H, s)

ESI/MS: 316 $[\text{M}+\text{Na}]^+$

5 Preparation 69

4-(3,4-Difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3,4-difluorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

10 IR (KBr): 3178, 1654, 1575, 1465, 1282 cm^{-1}

NMR (DMSO- d_6 , δ): 4.03(3H, s), 7.06-7.47(7H, m), 8.51(1H, s)

ESI/MS: 316 $[\text{M}+\text{H}]^+$, 388 $[\text{M}+\text{Na}]^+$

Preparation 70

15 4-(3,4-Dimethoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3,4-dimethoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3174, 1644, 1587, 1465, 1265 cm^{-1}

NMR (DMSO- d_6 , δ): 3.59(3H, s), 3.74(3H, s), 4.03(3H, s), 6.74-7.14(7H, m), 8.43(1H, s)

20 ESI/MS: 340 $[\text{M}+\text{H}]^+$, 362 $[\text{M}+\text{Na}]^+$

Preparation 71

25 4-(3,4-Dichlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3,4-dichlorophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3318, 1629, 1583, 1461, 1294 cm^{-1}

NMR (DMSO- d_6 , δ): 4.03(3H, s), 7.06-7.44(6H, m), 7.09(1H, d, $J=9.0$ Hz), 7.14(1H, d, $J=8.2$ Hz), 7.18(2H, s), 7.33(1H, d, $J=9.0$ Hz), 7.56(1H, d, $J=8.2$ Hz), 7.65(1H, s), 8.52(1H, s)

30 ESI/MS: 348, 350 and 352 $[\text{M}+\text{H}]^+$, 370, 372 and 374 $[\text{M}+\text{Na}]^+$

Preparation 72

5-(6-Methoxy-3-pyridazinyl)-4-(2-methylphenyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(2-methylphenyl)ethanone according to a similar manner to that of Preparation 60.

- 5 IR (KBr): 3120, 1630, 1580, 1465, 1250 cm^{-1}
NMR (DMSO- d_6 , δ): 1.98(3H, s), 3.99(3H, s), 6.85-7.31(6H, m), 7.06(2H, s), 8.60(1H, s)
ESI/MS: 294 $[\text{M}+\text{H}]^+$, 316 $[\text{M}+\text{Na}]^+$

Preparation 73

- 10 4-(2-Methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(2-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

IR(KBr): 3127, 1634, 1580, 1455, 1267 cm^{-1}

- 15 NMR (DMSO- d_6 , δ): 3.28(3H, s), 3.98(3H, s), 6.88(1H, d, $J=8.6$ Hz), 7.01(2H, brs), 7.02-7.05(3H, m), 7.34-7.42(2H, m)
ESI/MS: 310 $[\text{M}+\text{H}]^+$, 332 $[\text{M}+\text{Na}]^+$

Preparation 74

- 20 5-(6-Methoxy-3-pyridazinyl)-4-(2-thienyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(2-thienyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3124, 1637, 1575, 1458, 1285 cm^{-1}

- 25 NMR (DMSO- d_6 , δ): 4.05(3H, s), 6.55-6.58(1H, m), 6.77(1H, d, $J=3.6$ Hz), 7.01(2H, s), 7.21(1H, d, $J=9.2$ Hz), 7.49(1H, d, $J=9.2$ Hz), 7.66-7.67(1H, m), 8.33(1H, s)

ESI/MS: 286 $[\text{M}+\text{H}]^+$, 308 $[\text{M}+\text{Na}]^+$

Preparation 75

- 30 5-(6-Methoxy-3-pyridazinyl)-4-(3-methylphenyl)-2-pyrimidinamine was prepared from 2-(6-methoxy-3-pyridazinyl)-1-(3-methylphenyl)ethanone according to a similar manner to that of Preparation 60.

IR (KBr): 3135, 1625, 1585, 1466, 1260 cm^{-1}

NMR (DMSO- d_6 , δ): 2.26(3H, s), 4.03(3H, s), 6.91-7.37(8H, m), 8.48(1H, s)

ESI/MS: 294 $[\text{M}+\text{H}]^+$, 316 $[\text{M}+\text{Na}]^+$

5 Preparation 76

4-(3-Methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine was prepared from 1-(3-methoxyphenyl)-2-(6-methoxy-3-pyridazinyl)ethanone according to a similar manner to that of Preparation 60.

10 IR (KBr): 3140, 1627, 1568, 1465, 1240 cm^{-1}

NMR (DMSO- d_6 , δ): 2.29(3H, s), 4.03(sH, s), 7.00-7.21(8H, m), 8.45(1H, s)

ESI/MS: 310 $[\text{M}+\text{H}]^+$, 332 $[\text{M}+\text{Na}]^+$

Preparation 77

15 Carbon disulfide (0.248 ml) was dropwise added to a solution of 2-isopropyl-6-(2-oxo-2-phenyl-ethyl)-3(2H)-pyridazinone (1.00 g) and sodium hydroxide (343 mg) in a mixture of water (1.15 ml) and dimethyl sulfoxide (5 ml) at 5°C. After 30 minutes, iodomethane (0.607 ml) was dropwise added to the mixture at
20 5°C and the mixture was stirred at the same temperature for 2 hours. The mixture was poured into water (25 ml) and stirred for 1 hour to give a solid. The solid was dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column
25 chromatography on silica gel (n-hexane - ethyl acetate 60 : 40 v/v) to give 6-[1-benzoyl-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.23 g).

mp: 103-104.5°C (chloroform - n-hexane)

IR (KBr): 1670, 1581 cm^{-1}

30 ESI/MS: 743 $[2\text{M}+\text{Na}]^+$, 383 $[\text{M}+\text{Na}]^+$, 361 $[\text{M}+\text{H}]^+$

^1H NMR (CDCl_3 , δ): 1.17(6H, d, $J=6.66$ Hz), 2.17(3H, s), 2.42(3H, s), 5.22(1H, 7-plet, $J=6.66$ Hz), 6.84(1H, d, $J=9.82$ Hz),

7.41-7.57 (3H, m), 7.69 (1H, d, $J=9.82$ Hz), 7.89-7.94 (2H, m)

Elemental Analysis for $C_{18}H_{20}N_2O_2S_2$

Calcd.: C, 59.97; H, 5.59; N, 7.77

Found : C, 60.08; H, 5.58; N, 7.78

5 Preparation 78

6-[1-Benzoyl-2,2-bis(methylthio)vinyl]-2-methyl-3(2H)-pyridazinone was prepared from 2-methyl-6-(2-oxo-2-phenylethyl)-3(2H)-pyridazinone, carbon disulfide and methyl iodide according to a similar manner to that of Preparation 77.

mp: 143-146°C (chloroform - hexane)

IR (KBr): 1662, 1581 cm^{-1}

ESI/MS: 687[2M+Na]⁺, 355[M+Na]⁺, 333[M+H]⁺

¹H NMR (CDCl₃, δ): 2.14 (3H, s), 2.41 (3H, s), 3.71 (3H, s), 6.87 (1H, d, $J=9.70$ Hz), 7.43-7.58 (3H, m), 7.65 (1H, d, $J=9.70$ Hz), 7.90-7.96 (2H, m)

Elemental Analysis for $C_{16}H_{16}N_2O_2S_2 \cdot 0.3H_2O$

Calcd.: C, 56.88; H, 4.95; N, 8.29

Found : C, 56.83; H, 4.76; N, 8.36

20 Preparation 79

6-[1-(4-fluorobenzoyl)-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone, carbon disulfide and methyl iodide according to a similar manner to that of Preparation 77.

mp: 92-94°C (diisopropyl ether)

IR (KBr): 1678-1660, 1597, 1583 cm^{-1}

ESI/MS: 779[2M+Na]⁺, 401[M+Na]⁺

¹H NMR (CDCl₃, δ): 1.17 (6H, d, $J=6.60$ Hz), 2.18 (3H, s), 2.42 (3H, s), 5.23 (1H, 7-plet, $J=6.60$ Hz), 6.85 (1H, d, $J=9.64$ Hz), 7.11-7.18 (2H, m), 7.69 (1H, d, $J=9.64$ Hz), 7.92-7.98 (2H, m)

Preparation 80

1-(4-Bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone
was prepared according to a similar manner to that of Preparation
15.

¹H NMR (DMSO-d₆, δ): 4.00 (3H, s), 4.69 (2H, s), 7.21 (1H, d, J=9.0
5 Hz), 7.58 (1H, d, J=9.0 Hz), 7.78 (2H, d, J=8.6 Hz), 7.99 (2H,
d, J=8.6 Hz)

ESI/MS: 307, 309[M+H]⁺, 329, 331[M+Na]⁺

IR (KBr): 1639, 1585, 1465, 1012 cm⁻¹

Preparation 81

10 1-(3-Bromophenyl)-2-(6-methoxy-3-pyridazinyl)ethanone.
was prepared according to a similar manner to that of Preparation
15

¹H NMR (DMSO-d₆, δ): 4.00 (3H, s), 4.69 (2H, s), 7.21 (1H, d, J=9.0
Hz), 7.58 (1H, d, J=9.0 Hz), 7.78 (2H, d, J=8.6 Hz), 7.99 (2H,
15 d, J=8.6 Hz),

ESI/MS: 307, 309[M+H]⁺, 329, 331[M+Na]⁺

IR (KBr): 1641, 1558, 1467, 1010 cm⁻¹

Preparation 82

1-(2,6-Difluorophenyl)-2-(6-methoxy-3-pyridazinyl)
20 ethanone was prepared according to a similar manner to that
of Preparation 15.

¹H NMR (DMSO-d₆, δ): 4.00 (3H, s), 4.55 (2H, s), 7.14-7.34 (3H,
m), 7.43-7.72 (2H, m)

ESI/MS: 265[M+H]⁺, 287[M+Na]⁺

25 IR (neat): 1648, 1558, 1484 cm⁻¹

Preparation 83

1-(3,5-Difluorophenyl)-2-(6-methoxy-3-pyridazinyl)
ethanone was prepared according to a similar manner to that
of Preparation 15.

30 ¹H NMR (DMSO-d₆, δ): 4.00 (3H, s), 4.72 (2H, s), 7.22 (9.2H, d),
7.31-7.79 (4H, m)

ESI/MS: 265[M+H]⁺, 287[M+Na]⁺

IR (KBr): 1621, 1594, 1473, 1120 cm^{-1}

Preparation 84

1-(2,6-Dichlorophenyl)-2-(6-methoxy-3-pyridazinyl)
ethanone was prepared according to a similar manner to that
5 of Preparation 15.

^1H NMR ($\text{DMSO}-d_6$, δ): 4.02 (3H, s), 4.52 (2H, s), 7.21-7.64 (5H, m)

ESI/MS: 297, 299 $[\text{M}+\text{H}]^+$, 319, 321 $[\text{M}+\text{Na}]^+$

IR (KBr): 1621, 1594, 1473, 1018 cm^{-1}

10 Preparation 85

1-(2,6-Dimethylphenyl)-2-(6-methoxy-3-pyridazinyl)
ethanone was prepared according to a similar manner to that
of Preparation 15.

^1H NMR ($\text{DMSO}-d_6$, δ): 2.24 (3H, s), 2.28 (3H, s), 4.02 (2H, s),
15 7.07-7.30 (4H, m), 7.52 (1H, m)

ESI/MS: 257 $[\text{M}+\text{H}]^+$, 279 $[\text{M}+\text{Na}]^+$

IR (KBr): 1643, 1540, 1311, 1012 cm^{-1}

Preparation 86

1-(3-Furyl)-2-(6-methoxy-3-pyridazinyl)ethanone was
20 prepared according to a similar manner to that of Preparation
15.

^1H NMR (CDCl_3 , δ): 4.12 (3H, s), 4.36 (2H, s), 6.805 (1H, d, $J=2$
Hz), 6.88 (1H, d, $J=9.4$ Hz), 7.41-7.46 (2H, m), 8.26 (1H, s),

ESI/MS: 219.3 $[\text{M}+\text{H}]^+$, 241.1 $[\text{M}+\text{Na}]^+$

25 IR (KBr): 1678, 1598, 1471, 1153 cm^{-1}

Preparation 87

2-(6-Methoxy-3-pyridazinyl)-1-(3-thienyl)ethanone was
prepared according to a similar manner to that of Preparation
15.

30 ^1H NMR (CDCl_3 , δ): 4.11 (3H, s), 4.42 (2H, s), 6.73 (1H, d, $J=2$
Hz), 6.96 (1H, d, $J=9.6$ Hz), 7.41-7.46 (2H, m), 8.40 (1H, s)

ESI/MS: 235.1 $[\text{M}+\text{H}]^+$, 257.2 $[\text{M}+\text{Na}]^+$

IR (KBr): 1668, 1602, 1473, 1014 cm^{-1}

Preparation 88

1-(2,6-Dimethoxyphenyl)-2-(6-methoxy-3-pyridazinyl)
ethanone was prepared according to a similar manner to that
5 of Preparation 43.

^1H NMR (DMSO- d_6 , δ): 3.75(6H, s), 4.05(3H, s), 4.28(2H, s),
6.71(2H, d, $J=8.4$ Hz), 7.18(1H, d, $J=9.2$ Hz), 7.33(1H, d, $J=8.4$
Hz), 7.42(1H, d, $J=9.2$ Hz)

ESI/MS: 289[M+H] $^+$, 311[M+Na] $^+$

10 IR (KBr): 1716, 1592, 1473, 1110 cm^{-1}

Preparation 89

4-(4-Bromophenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

15 ^1H NMR (DMSO- d_6 , δ): 4.02(3H, s), 7.10(2H, s), 7.07-7.26(2H,
m), 7.23(2H, d, $J=8.6$ Hz), 7.54(2H, d, $J=8.6$ Hz), 8.69(1H,
s)

ESI/MS: 358, 360[M+H] $^+$, 380, 382[M+Na] $^+$

IR (KBr): 3326, 1629, 1583, 1463 cm^{-1}

20 Preparation 90

4-(3-Bromophenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

25 ^1H NMR (DMSO- d_6 , δ): 4.03(3H, s), 7.10(1H, d, $J=9.0$ Hz), 7.15(2H,
s), 7.25(1H, d, $J=9.0$ Hz), 7.21-7.61(2H, m), 7.56-7.60(2H,
m), 8.51(1H, s),

ESI/MS: 358, 360[M+H] $^+$, 380[M+Na] $^+$

IR (KBr): 3318, 1627, 1529, 1461 cm^{-1}

Preparation 91

30 4-(2,6-Difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

^1H NMR (DMSO- d_6 , δ): 3.96(3H, s), 7.13(1H, d, $J=9.2$ Hz),
7.06-7.14(2H, m), 7.22(2H, s), 7.46(1H, d, $J=9.2$ Hz),
7.42-7.60(1H, m), 8.64(1H, s)
ESI/MS: 316[M+H] $^+$, 338[M+Na] $^+$

5 Preparation 92

4-(3,5-Difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

^1H NMR (DMSO- d_6 , δ): 4.03(3H, s), 6.93-6.98(2H, m), 7.14(1H,
10 d, $J=9.2$ Hz), 7.18(2H, s), 7.32(1H, d, $J=9.2$ Hz), 7.24-7.37(1H,
m), 8.54(1H, s)

ESI/MS: 316[M+H] $^+$, 338[M+Na] $^+$

IR (KBr): 3478, 1627, 1581, 1459 cm^{-1}

Preparation 93

15 4-(2,6-Dichlorophenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

^1H NMR (DMSO- d_6 , δ): 3.96(3H, s), 7.12(1H, d, $J=9.4$ Hz), 7.22(2H,
s), 7.33(1H, d, $J=9.4$ Hz), 7.30-7.52(3H, m), 8.69(1H, s)

20 ESI/MS: 348, 350[M+H] $^+$, 370, 372[M+Na] $^+$

IR (KBr): 3309, 1621, 1581, 1459 cm^{-1}

Preparation 94

25 4-(2,6-Dimethylphenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

^1H NMR (DMSO- d_6 , δ): 1.93(6H, s), 3.97(3H, s), 6.84-7.20(5H,
m), 8.64(1H, s)

ESI/MS: 308[M+H] $^+$, 330[M+Na] $^+$

IR (KBr): 3309, 1621, 1581, 1459 cm^{-1}

30 Preparation 95

4-(3-Furyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner

to that of Preparation 60.

^1H NMR (DMSO- d_6 , δ): 4.07(3H, s), 6.32(1H, s), 6.94(2H, s), 7.21(1H, d, $J=9.2$ Hz), 7.52(1H, d, $J=9.2$ Hz), 7.55(1H, s), 7.64(1H, s), 8.31(1H, s)

5 ESI/MS: 270[M+H] $^+$, 292[M+Na] $^+$

IR (KBr): 3168, 1652, 1581, 1461 cm^{-1}

Preparation 96

5-(6-Methoxy-3-pyridazinyl)-4-(3-thienyl)-
2-pyrimidinamine was prepared according to a similar manner
10 to that of Preparation 60.

^1H NMR (DMSO- d_6 , δ): 4.05(3H, s), 6.94-6.97(3H, m), 7.13(1H, d, $J=9.2$ Hz), 7.28(1H, d, $J=9.2$ Hz), 7.46-7.52(2H, m), 8.39(1H, s)

APCI/MS: 286[M+H] $^+$

15 IR (KBr): 3191, 1656, 1581, 1461 cm^{-1}

Preparation 97

4-(2,6-Dimethoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-
2-pyrimidinamine was prepared according to a similar manner
to that of Preparation 60.

20 ^1H NMR (DMSO- d_6 , δ): 3.55(6H, s), 3.97(3H, s), 6.64(2H, d, $J=8.6$ Hz), 6.91(2H, s), 6.96-7.02(2H, m), 7.31(1H, t, $J=5.6$ Hz), 8.52(1H, s)

ESI/MS: 340[M+H] $^+$, 340[M+Na] $^+$

IR (KBr): 3309, 1621, 1581, 1459 cm^{-1}

25 Example 1

A mixture of 2-amino-5-(6-methoxy-3-pyridazinyl)-4-phenylpyrimidine (5.41 g), conc. HCl (0.1 ml) and 4N HCl/dioxane (48.5 ml) in dioxane (54 ml) was heated to 110°C for 1.5 hours. The reaction mixture was poured into ice/water and pH was adjusted
30 to circa 7-8 with aqueous sodium hydroxide solution. Precipitates were collected by filtration, washed with water and dried to give a crude material, which was recrystallized from 90% aqueous

EtOH to give

6-(2-amino-4-phenyl-5-pyrimidinyl)-3(2H)-pyridazinone (4.34 g) as colorless crystals.

mp: > 280°C

5 IR (Nujol): 3269, 1676, 1651 cm^{-1}

NMR (DMSO- d_6 , δ): 6.67(1H, d, $J=9.8$ Hz), 6.87(1H, d, $J=9.8$ Hz), 7.04(2H, brd. s), 7.37-7.44(5H, m), 8.39(1H, s), 13.07(1H, s),

ESI/MS: 288 $[\text{M}+\text{Na}]^+$

10 Elemental Analysis for $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}$

Calcd.: C, 63.39; H, 4.18; N, 26.40

Found : C, 63.55; H, 4.24; N, 26.32

Example 2

A suspension of 6-(2-amino-4-phenyl-5-pyrimidinyl)-3(2H)-pyridazinone (503 mg) in DMF (10 ml) was cooled in an ice/water bath and 60% NaH (83.9 mg) was added to the mixture. After the mixture was stirred for 15 minutes, isopropyl iodide was added and the mixture was stirred at ambient temperature overnight. The mixture was poured into ice/water and resultant precipitates were filtered, washed with water, and dried to give 430 mg of powder, which was then purified by silica-gel column chromatography (CHCl_3 -MeOH, 50:1) to give 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (354 mg) as colorless crystals.

25 mp: 216-217°C (90% aqueous EtOH)

IR (Nujol): 3356, 3313, 3170, 1671, 1651 cm^{-1}

NMR (DMSO- d_6 , δ): 1.04(6H, d, $J=6.6$ Hz), 4.97-5.10(1H, m), 6.80(1H, d, $J=9.6$ Hz), 7.06(2H, brd. s), 7.18(1H, d, $J=9.6$ Hz), 7.31-7.41(5H, m), 8.46(1H, s)

30 ESI/MS: 330 $[\text{M}+\text{Na}]^+$

Elemental Analysis for $\text{C}_{17}\text{H}_{17}\text{N}_5\text{O}$

Calcd.: C, 66.43; H, 5.58; N, 22.79

Found : C, 66.17; H, 5.58; N, 22.69

Example 3

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

- 5 mp: 254-255°C (90% aqueous EtOH)
IR (Nujol): 3313, 3168, 1670, 1649 cm^{-1}
NMR (DMSO- d_6 , δ): 3.65(3H, s), 6.71(1H, d, J=9.6 Hz), 6.83(1H, d, J=9.6 Hz), 7.08(2H, brd. s), 7.38-7.46 (5H, m), 8.42(1H, s)
10 ESI/MS: 302 $[\text{M}+\text{Na}]^+$
Elemental Analysis for $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}$
Calcd.: C, 64.51; H, 4.69; N, 25.08
Found : C, 64.32; H, 4.75; N, 24.91

15 Example 4

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-ethyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

- mp: 255-256°C (90% aqueous EtOH)
20 IR (Nujol): 1649 cm^{-1}
NMR (DMSO- d_6 , δ): 1.13(3H, t, J=7.2 Hz), 4.01(2H, q, J=7.2 Hz), 6.75(1H, d, J=9.6 Hz), 6.99(1H, d, J=9.6 Hz), 7.07(2H, brd. s), 7.35-7.43(5H, m), 8.44(1H, s)
ESI/MS: 316 $[\text{M}+\text{Na}]^+$
25 Elemental Analysis for $\text{C}_{16}\text{H}_{15}\text{N}_5\text{O}$
Calcd.: C, 65.52; H, 5.15; N, 23.88
Found : C, 65.48; H, 5.21; N, 23.78

Example 5

- 6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-propyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 188-189°C (90% aqueous EtOH)
IR (Nujol): 1651 cm^{-1}

NMR (DMSO-d₆, δ): 0.80 (3H, t, J=7.4 Hz), 1.48-1.66 (2H, m), 3.96 (2H, t, J=7.2 Hz), 6.75 (1H, d, J=9.6 Hz), 6.99 (1H, d, J=9.6 Hz), 7.07 (2H, brd. s), 7.34-7.43 (5H, m), 8.42 (1H, s)

ESI/MS: 330 [M+Na]⁺

- 5 Elemental Analysis for C₁₇H₁₇N₅O
Calcd.: C, 66.43; H, 5.58; N, 22.79
Found : C, 66.25; H, 5.61; N, 22.72

Example 6

- 6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-benzyl-3(2H)-
10 pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 229-230°C (90% aqueous EtOH)

IR (Nujol): 3353, 3324, 3191, 1670, 1651 cm⁻¹

- NMR (DMSO-d₆, δ): 5.19 (2H, s), 6.80 (1H, d, J=9.6 Hz), 7.01 (1H,
15 d, J=9.6 Hz), 7.08 (2H, brd. s), 7.17-7.46 (10H, m), 8.38 (1H, s).

ESI/MS: 378 [M+Na]⁺

Elemental Analysis for C₂₁H₁₇N₅O

Calcd.: C, 70.97; H, 4.82; N, 19.71

- 20 Found : C, 70.85; H, 4.92; N, 19.68

Example 7

- A solution of 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-
isopropyl-3(2H)-pyridazinone (177 mg) in pyridine (1.8 ml)
was cooled in an ice/water bath. Acetyl chloride (49.7 mg)
25 was added to the solution and the mixture was stirred at ambient temperature for 4 hours. Pyridine was removed under reduced pressure and the residue was partitioned between water and CHCl₃. After an additional extraction with CHCl₃, the combined
extracts were washed with saturated sodium hydrogencarbonate
30 solution and brine, dried over MgSO₄, and concentrated under reduced pressure. The crude material was purified by silica-gel column chromatography (CHCl₃-MeOH, 50:1) to give
N-[5-(1-isopropyl-6-oxo-1,6-dihydro-

3-pyridazinyl)-4-phenyl-2-pyrimidinyl]acetamide (107 mg) as colorless crystals.

mp: 209-210°C (90% aqueous EtOH)

IR (Nujol): 3157, 3128, 1670, 1652 cm⁻¹

5 NMR (DMSO-d₆, δ): 1.04 (6H, d, J=6.6 Hz), 2.27 (3H, s), 5.02-5.08 (1H, m), 6.90 (1H, d, J=9.6 Hz), 7.34 (1H, d, J=9.6 Hz), 7.44 (5H, s), 8.85 (1H, s), 10.79 (1H, s),

ESI/MS: 349 [M+Na]⁺

Elemental Analysis for C₁₉H₁₉N₅O₂

10 Calcd.: C, 65.32; H, 5.48; N, 20.04

Found : C, 65.27; H, 5.53; N, 19.86

Example 8

6-[2-(Methylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone was obtained from 5-(6-methoxy-3-pyridazinyl)-N-methyl-4-phenyl-2-pyrimidinamine according to a similar manner to that of Example 1.

mp: >255°C (90% aqueous EtOH)

IR (Nujol): 3311, 1670, 1651 cm⁻¹

20 NMR (DMSO-d₆, δ): 2.89 (3H, d, J=4.7 Hz), 6.67 (1H, d, J=9.7 Hz), 6.87 (1H, d, J=9.7 Hz), 7.42-7.51 (6H, m), 8.43 (1H, brd. s), 13.07 (1H, brd. s)

ESI/MS: 302 [M+Na]⁺

Elemental Analysis for C₁₅H₁₃N₅O

Calcd.: C, 64.51; H, 4.69; N, 25.08

25 Found : C, 64.39; H, 4.72; N, 24.92

Example 9

6-[2-(Dimethylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone was obtained from 5-(6-methoxy-3-pyridazinyl)-N,N-dimethyl-4-phenyl-2-pyrimidinamine according to a similar manner to that of Example 1.

mp: 245-246°C (90% aqueous EtOH)

IR (Nujol): 3213, 1674, 1650 cm⁻¹

NMR (DMSO- d_6 , δ): 3.22(6H, s), 6.69(1H, d, $J=9.8$ Hz), 6.88(1H, d, $J=9.8$ Hz), 7.38-7.50(5H, m), 8.49(1H, s), 13.09(1H, brd. s)

ESI/MS: 316 $[M+Na]^+$

5 Elemental Analysis for $C_{16}H_{15}N_5O$

Calcd.: C, 65.52; H, 5.15; N, 23.88

Found : C, 65.44; H, 5.12; N, 23.85

Example 10

2-Isopropyl-6-[2-(methylamino)-4-phenyl-5-pyrimidinyl]-
10 3(2H)-pyridazinone was obtained from 6-[2-(methylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone according to a similar manner to that of Example 2.

mp: 160-161°C (EtOAc)

IR (Nujol): 1651 cm^{-1}

15 NMR (DMSO- d_6 , δ): 1.03(6H, d, $J=6.5$ Hz), 2.89(3H, d, $J=4.8$ Hz), 5.02-5.05(1H, m), 6.81(1H, d, $J=9.6$ Hz), 7.19(1H, d, $J=9.6$ Hz), 7.39(5H, brd. s), 7.54(1H, brd. s), 8.50(1H, brd. s)

ESI/MS: 322 $[M+H]^+$, 344 $[M+Na]^+$

Elemental Analysis for $C_{18}H_{19}N_5O$

20 Calcd.: C, 67.27; H, 5.96; N, 21.79

Found : C, 67.26; H, 6.01; N, 21.75

Example 11

6-[2-(Dimethylamino)-4-phenyl-5-pyrimidinyl]-2-
isopropyl-3(2H)-pyridazinone was obtained from 6-[2-
25 (dimethylamino)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone according to a similar manner to that of Example 2.

mp: 155-156°C (EtOAc)

IR (Nujol): 1650, 1590 cm^{-1}

NMR (DMSO- d_6 , δ): 1.03(6H, d, $J=6.6$ Hz), 3.22(6H, s), 5.02-5.05(1H, m), 6.83(1H, d, $J=9.6$ Hz), 7.20(1H, m, $J=9.6$ Hz), 7.40(5H, s), 8.56(1H, s).

ESI/MS: 336 $[M+H]^+$, 358 $[M+Na]^+$

Elemental Analysis for $C_{19}H_{21}N_5O$

Calcd.: C, 68.04; H, 6.31; N, 20.88

Found : C, 68.01; H, 6.34; N, 20.87

Example 12

5 6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was obtained from 2-isopropyl-6-(2-oxo-2-phenylethyl)-(2H)-pyridazinone according to a similar manner to that of Preparation 3.

mp: 216-217°C (90% aqueous EtOH).

10 Example 13

(1)

To a mixture of 6-[2-(4-fluorophenyl)-2-oxoethyl]-2-isopropyl-3(2H)-pyridazinone (1.65 g) and N,N-dimethylformamide dimethyl acetal (1.6 ml) was heated at
15 100-105°C for 30 minutes. The mixture was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (MeOH-EtOAc, 1:99 v/v) to give a stereomixture of

6-[2-(dimethylamino)-1-(4-fluorobenzoyl)-ethenyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.57 g).

mp: 161-162.5°C (chloroform - n-hexane)

IR (KBr) : 1647, 1626, 1581, 1552 cm^{-1}

1H NMR ($CDCl_3$, δ) : major product 1.32(6H, d, J=6.67 Hz), 2.90(6H, s), 5.33(1H, 7-plet, J=6.67 Hz), 6.76(1H, d, J=9.48 Hz),
25 6.95-7.11(3H, m), 7.43-7.52(3H, m);

minor product 1.24(6H, d, J=6.60 Hz), 2.99(6H, s)

ESI/MS: 681 $[2M+Na]^+$, 352 $[M+Na]^+$, 330 $[M+H]^+$

Elemental Analysis for $C_{18}H_{20}FN_3O_2$

Calcd.: C, 65.64; H, 6.12; N, 12.76

30 Found : C, 65.35; H, 6.38; N, 12.58

(2)

To a solution of potassium t-butoxide (80.8 mg) in methanol (0.6 ml), guanidine hydrochloride (68.8 mg) was added under

ice-cooling. After 15 minutes, a stereomixture of
6-[2-(dimethylamino)-1-(4-fluorobenzoyl)ethenyl]-2-isopropyl-
1,3(2H)-pyridazinone (198 mg) was added and heated under reflux
for 4 hours. Water was added to a reaction mixture. After stirring,
5 an aqueous layer was removed by decantation to give a residue.
The residue was dissolved in chloroform, dried over magnesium
sulfate, concentrated under reduced pressure and was
recrystallized from a mixture of chloroform and hexane to give
6-[2-amino-4-(4-fluorophenyl)-5-pyrimidinyl]-2-isopropyl-
10 3(2H)-pyridazinone as a solid (138 mg).

mp: 238-239°C (ethanol-isopropyl ether)

IR (KBr) : 3413, 3182, 1647, 1577, 1492 cm^{-1}

^1H NMR (CDCl_3 , δ) : 1.31(6H, d, $J=6.62$ Hz), 5.33(1H, 7-plet,
 $J=6.62$ Hz), 5.37(2H, br.s), 6.70(1H, d, $J=9.56$ Hz), 6.74(1H,
15 d, $J=9.56$ Hz), 7.05-7.10(2H, m), 7.40-7.45(2H, m), 8.51(1H,
s)

ESI/MS: 673 $[\text{2M}+\text{Na}]^+$, 348 $[\text{M}+\text{Na}]^+$, 326 $[\text{M}+\text{H}]^+$

Elemental Analysis for $\text{C}_{17}\text{H}_{16}\text{FN}_5\text{O}$

Calcd.: C, 62.76; H, 4.96; N, 21.53

20 Found : C, 62.76; H, 4.90; N, 21.54

Example 14

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-3(2H)-
pyridazinone was obtained according to a similar manner to
that of Example 1.

25 NMR ($\text{DMSO}-d_6$, δ): 6.68(1H, d, $J=9.8$ Hz), 6.95(1H, d, $J=9.8$ Hz),
7.14(2H, brd. s), 7.32-7.47(3H, m), 7.63(1H, d, $J=7.9$ Hz),
8.50(1H, s), 13.0(1H, brd. s)

ESI/MS: 366, 368 $[\text{M}+\text{Na}]^+$

Example 15

30 6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-isopropyl-
3(2H)-pyridazinone was obtained according to a similar manner
to that of Example 2.

mp: 203-205°C (EtOH)

IR (Nujol): 3396, 3319, 3197, 1649, 1630, 1579, 1560 cm^{-1}
NMR (DMSO-d_6 , δ): 0.86(6H, d, $J=6.4$ Hz), 4.87-5.00(1H, m), 6.85(1H, d, $J=9.7$ Hz), 7.15(2H, brd. s), 7.29-7.58(4H, m), 7.60(1H, d, $J=7.4$ Hz), 8.57(1H, s)

5 ESI/MS: 408, 410 $[\text{M}+\text{Na}]^+$

Example 16

A suspension of 6-[2-amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (138 mg), 10% palladium on carbon (19.7 mg) and sodium acetate (58.6 mg)
10 in methanol(14 ml) was hydrogenated at 20°C under hydrogen atmosphere for 8 hours. Insoluble material was filtered off and the solvent was removed under reduced pressure. The residue was partitioned between sodium bicarbonate solution and dichloromethane. After additional extraction with
15 dichloromethane (x2), the combined extracts were washed with water, dried over MgSO_4 and concentrated under reduced pressure to afford colorless crystals of 6-(2-amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone.

Example 17

20 A solution of 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone (177 mg) and morpholine (0.0653 ml) in dioxane (0.35 ml) was heated at 100-105°C for 25 hours. Water (3.5 ml) was added to the reaction mixture to give a solid. The solid was collected by filtration, dissolved
25 in chloroform, dried over magnesium sulfate and purified by column chromatography on silica gel (methanol - chloroform 1 : 99 v/v) to give 2-isopropyl-6-[2-morpholino-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone as a solid (125 mg).
30 mp: 200.5-202°C (ethanol - diisopropyl ether)
IR (KBr): 1666, 1591, 1574, 1514 cm^{-1}
 ^1H NMR (CDCl_3 , δ) : 1.31(6H, d, $J=6.64$ Hz), 3.77-3.83(4H, m), 3.91-3.97(4H, m), 5.31(1H, 7-plet, $J=6.64$ Hz), 6.66(1H, d,

J=9.54 Hz), 6.71(1H, d, J=9.54 Hz), 7.33-7.48(5H, m), 8.56(1H, s)

ESI/MS: 777 [2M+Na]⁺, 400 [M+Na]⁺, 378 [M+H]⁺

Elemental Analysis for C₂₁H₂₃N₅O₂

5 Calcd.: C, 66.83; H, 6.14; N, 18.55

Found : C, 66.84; H, 6.33; N, 18.48

Example 18

2-Isopropyl-6-{4-phenyl-2-[(2-pyridinylmethyl)amino]-5-pyrimidinyl}-3(2H)-pyridazinone was prepared from 2-isopropyl-
10 6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone and 2-pyridinylmethylamine according to a similar manner to that of Example 17.

mp: 143-144.5°C (ethanol - diisopropyl ether)

IR (KBr): 3275, 1660, 1587, 1576 cm⁻¹

15 ¹H NMR (CDCl₃, δ) : 1.31(6H, d, J=6.62 Hz), 4.86(2H, d, J=5.46 Hz), 5.31(1H, 7-plet, J=6.62 Hz), 6.45-6.49(1H, m), 6.66(1H, d, J=9.60 Hz), 6.70(1H, d, J=9.60 Hz), 7.17-7.24(1H, m), 7.33-7.68(6H, m), 7.63-7.73(1H, m), 8.55-8.61(2H, m)

ESI/MS: 421 [M+Na]⁺, 399 [M+H]⁺

20 Elemental Analysis for C₂₃H₂₂N₆O·0.2H₂O

Calcd.: C, 68.71; H, 5.62; N, 20.90

Found : C, 68.65; H, 5.65; N, 20.88

Example 19

6-(2-Anilino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-
25 pyridazinone was prepared from 2-isopropyl-6-[2-(methylsulfinyl)-4-phenyl-5-pyrimidinyl]-3(2H)-pyridazinone and aniline according to a similar manner to that of Example 17.

mp: 200-202°C (ethanol - diisopropyl ether)

30 IR (KBr): 1662, 1587, 1568 cm⁻¹

¹H NMR (CDCl₃, δ) : 1.33(6H, d, J=6.62 Hz), 5.32(1H, 7-plet, J=6.62 Hz), 6.69(1H, d, J=9.55 Hz), 6.74(1H, d, J=9.55 Hz),

7.08 (1H, t, J=7.42 Hz), 7.32-7.52 (9H, m), 7.70 (1H, d, J=7.68 Hz), 8.66 (1H, s)

ESI/MS: 789 [2M+Na]⁺, 406 [M+Na]⁺, 384 [M+H]⁺

Elemental Analysis for C₂₃H₂₁N₅O

5 Calcd.: C, 72.04; H, 5.52; N, 18.26

Found : C, 71.88; H, 5.58; N, 18.17

Example 20

6-[2-Amino-4-(2-fluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(2-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 239-240.5°C (ethanol)

IR (KBr): 3392, 3325, 3203, 1649, 1633, 1585 cm⁻¹

15 ¹H NMR (CDCl₃, δ) : 1.11 (6H, d, J=6.60 Hz), 5.20 (1H, 7-plet, J=6.60 Hz), 5.45 (2H, br.s), 6.79 (1H, d, J=9.56 Hz), 6.94-7.04 (2H, m), 7.20-7.55 (3H, m), 8.51 (1H, s)

ESI/MS: 673 [2M+Na]⁺, 348 [M+Na]⁺, 326 [M+H]⁺

Elemental Analysis for C₁₇H₁₆FN₅O

20 Calcd.: C, 62.76; H, 4.96; N, 21.53

Found : C, 62.74; H, 5.07; N, 21.39

Example 21

6-[2-Amino-4-(3-fluorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(3-fluorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride according to a similar manner to that of Example 13(2).

mp: 220-221.5°C (ethanol)

IR (KBr): 3425, 3305, 3194, 1660, 1637, 1581 cm⁻¹

30 ¹H NMR (CDCl₃, δ) : 1.29 (6H, d, J=6.60 Hz), 5.30 (1H, 7-plet, J=6.60 Hz), 5.39 (2H, br.s), 6.73 (1H, d, J=9.56 Hz), 6.78 (1H, d, J=9.56 Hz), 7.09-7.33 (4H, m), 8.53 (1H, s)

ESI/MS: 673 [2M+Na]⁺, 348 [M+Na]⁺, 326 [M+H]⁺

Elemental Analysis for $C_{17}H_{16}FN_5O$

Calcd.: C, 62.76; H, 4.96; N, 21.53

Found : C, 62.77; H, 5.02; N, 21.55

Example 22

5 6-[2-Amino-4-(2-chlorophenyl)-5-pyrimidinyl]-2-isopropyl
1-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(
(2-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and
guanidine hydrochloride according to a similar manner to that
of Example 13(2).

10 mp: 227-228.5°C (ethanol)

IR (KBr): 3398, 3327, 3201, 1649, 1631 cm^{-1}

1H NMR (DMSO- d_6 , δ): 0.85(6H, d, $J=6.58$ Hz), 5.30(1H, 7-plet,
 $J=6.58$ Hz), 6.86(1H, d, $J=9.58$ Hz), 7.15(2H, br.s), 7.33-(4H,
m), 7.48(1H, d, $J=9.58$ Hz), 8.57(1H, s)

15 ESI/MS: 707 and 705 $[2M+Na]^+$, 366 and 364 $[M+Na]^+$,
344 and 342 $[M+H]^+$ (mobile phase MeOH- H_2O)

Elemental Analysis for $C_{17}H_{16}ClN_5O$

Calcd.: C, 59.74; H, 4.72; N, 20.49

Found : C, 59.92; H, 4.79; N, 20.45

20 Example 23

6-[2-Amino-4-(3-chlorophenyl)-5-pyrimidinyl]-2-isopropyl
-3(2H)-pyridazinone was prepared from 6-[2-(dimethylamino)-1-(
(3-chlorobenzoyl)ethenyl]-2-isopropyl-3(2H)-pyridazinone and
guanidine hydrochloride according to a similar manner to that
25 of Example 13(2).

mp: 236-237°C (ethanol)

IR (KBr): 3471, 3298, 3180, 1664, 1622, 1585 cm^{-1}

1H NMR (CDCl $_3$, δ) : 1.28(6H, d, $J=6.62$ Hz), 5.30(1H, 7-plet,
 $J=6.62$ Hz), 5.37(2H, br.s), 6.74(1H, d, $J=9.54$ Hz), 6.79(1H,
30 d, $J=9.54$ Hz), 7.17-7.42(3H, m), 7.51-7.53(1H, m), 8.53(1H,
s)

ESI/MS: 707 and 705 $[2M+Na]^+$, 366 and 364 $[M+Na]^+$,
344 and 342 $[M+H]^+$

Elemental Analysis for $C_{17}H_{16}ClN_5O$

Calcd.: C, 59.74; H, 4.72; N, 20.49

Found : C, 59.58; H, 4.76; N, 20.41

Example 24

5 6-{2-Amino-4-[2-(trifluoromethyl)phenyl]-5-pyrimidinyl}
-2-isopropyl-3(2H)-pyridazinone was prepared from
6-{2-(dimethylamino)-1-[2-(trifluoromethyl)benzoyl]-ethenyl
}-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride
according to a similar manner to that of Example 13(2).

10 mp: 160-161°C (ethanol - hexane)

IR (KBr): 3411, 3329, 3207, 1649, 1630, 1583 cm^{-1}

1H NMR ($CDCl_3$, δ) : 1.07(6H, d, $J=6.62$ Hz), 5.18(1H, 7-plet,
 $J=6.62$ Hz), 5.35(2H, br.s), 6.73(1H, d, $J=9.56$ Hz), 6.92(1H,
d, $J=9.56$ Hz), 7.24-7.29(1H, m), 7.47-7.61(2H, m), 7.71-7.77(1H,
15 m), 8.57(1H, s)

ESI/MS: 773 $[2M+Na]^+$, 398 $[M+Na]^+$

Elemental Analysis for $C_{18}H_{16}F_3N_5O$

Calcd.: C, 57.60; H, 4.30; N, 18.66

Found : C, 57.86; H, 4.29; N, 18.72

20 Example 25

6-{2-Amino-4-[3-(trifluoromethyl)phenyl]-5-pyrimidinyl}
-2-isopropyl-3(2H)-pyridazinone was prepared from
6-{2-(dimethylamino)-1-[3-(trifluoromethyl)benzoyl]-ethenyl
}-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride
25 according to a similar manner to that of Example 13(2).

mp: 163.5-165°C (ethanol - hexane)

IR (KBr): 3454, 3305, 3178, 1662, 1630, 1585 cm^{-1}

1H NMR ($CDCl_3$, δ) : 1.23(6H, d, $J=6.62$ Hz), 5.28(1H, 7-plet,
 $J=6.62$ Hz), 5.41(2H, br.s), 6.75(1H, d, $J=9.56$ Hz), 6.82(1H,
30 d, $J=9.56$ Hz), 7.44-7.57(2H, m), 7.65-7.69(1H, m), 7.78(1H,
br.s), 8.53(1H, s)

ESI/MS: 773 $[2M+Na]^+$, 398 $[M+Na]^+$, 376 $[M+H]^+$

Elemental Analysis for $C_{18}H_{16}F_3N_5O$

Calcd.: C, 57.60; H, 4.30; N, 18.66

Found : C, 57.67; H, 4.36; N, 18.52

Example 26

- 6-{2-Amino-4-[4-(trifluoromethyl)phenyl]-5-pyrimidinyl}-
5 -2-isopropyl-3(2H)-pyridazinone was prepared from
6-{2-(dimethylamino)-1-[4-(trifluoromethyl)benzoyl]-ethenyl
}-2-isopropyl-3(2H)-pyridazinone and guanidine hydrochloride
according to a similar manner to that of Example 13(2).
mp: 209-210.5°C (ethanol - hexane)
10 IR (KBr): 3338, 3311, 3180, 1643, 1583 cm⁻¹
¹H NMR (CDCl₃, δ) : 1.20(6H, d, J=6.62 Hz), 5.27(1H, 7-plet,
J=6.62 Hz), 5.42(2H, br.s), 6.76(1H, d, J=9.54 Hz), 6.84(1H,
d, J=9.54 Hz), 7.53(2H, d, J=8.26 Hz), 7.65(2H, d, J=8.26 Hz),
8.54(1H, s)
15 ESI/MS: 773 [2M+Na]⁺, 398 [M+Na]⁺, 376 [M+H]⁺
Elemental Analysis for C₁₈H₁₆F₃N₅O
Calcd.: C, 57.60; H, 4.30; N, 18.66
Found : C, 57.81; H, 4.29; N, 18.79

Example 27

- 20 4-(4-Methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-
pyrimidinamine (309 mg) was dissolved in c-hydrochloric acid
(5 ml) and dioxane (20 ml). The solution was heated at 55°C,
and stirred overnight. Evaporation of solvent in vacuo gave
a residue. To the residue was added water (10 ml). The pH of
25 the suspension was adjusted to 7-8 with 1N-sodium hydroxide
solution. The crystals were collected by filtration, washed
with water, dried in vacuo, to give
6-[2-amino-4-(4-methoxyphenyl)-5-
pyrimidinyl]-3(2H)-pyridazinone (285 mg).
30 mp: 142°C (water)
IR (KBr): 3409, 1639, 1585, 1251 cm⁻¹
NMR (DMSO-d₆, δ): 3.78(3H, s), 6.95(1H, d, J=9.8 Hz), 6.89(1H,
d, J=9.8 Hz), 6.97(1H, d, J=9.0 Hz), 6.99(1H, s), 7.36(1H,

d, J=9.0 Hz), 8.33(1H, s), 13.1(1H, s)

ESI/MS: 296 [M+H]⁺

Example 28

5 6-[2-Amino-4-(3-fluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3-fluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 249°C (water)

10 IR (KBr): 3156, 1677, 1577, 1440, 1263 cm⁻¹

NMR (DMSO-d₆, δ): 6.73(1H, d, J=9.8 Hz), 6.98(1H, d, J=9.8 Hz), 7.12-7.45(7H, m), 8.42(1H, s), 13.1(1H, s)

ESI/MS: 284 [M+H]⁺

Example 29

15 6-[2-Amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3-fluoro-4-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 250°C (water)

20 IR (KBr): 3164, 1654, 1550, 1417, 1238 cm⁻¹

NMR (DMSO-d₆, δ): 3.85(3H, s), 6.73(1H, d, J=9.8 Hz), 6.98(1H, d, J=9.8 Hz), 7.06(2H, s), 7.14-7.36(4H, m), 8.36(1H, s), 13.1(1H, s)

ESI/MS: 314 [M+H]⁺

25 Example 30

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(4-chlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

30 IR (KBr): 3317, 1630, 1566, 1481, 1228 cm⁻¹

NMR (DMSO-d₆, δ): 6.74(1H, d, J=9.8 Hz), 6.97(1H, d, J=9.8 Hz),

7.11(1H, s), 7.32-7.51(4H, m), 8.40(1H, s), 13.1(1H, s)

ESI/MS: 300 and 302 [M+H]⁺

Example 31

- 5 6-[2-Amino-4-(3-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(3-pyridinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 256°C (water)

IR (KBr): 3170, 1646, 1550, 1409, 1220 cm⁻¹

- 10 NMR (DMSO-d₆, δ): 6.76(1H, d, J=9.8 Hz), 7.09(1H, d, J=9.8 Hz), 7.16(2H, s), 7.40-7.48(1H, m), 7.73-7.79(1H, m), 8.44(1H, s), 8.57-8.61(2H, m), 13.1(1H, brs)

ESI/MS: 265 [M-H]⁻

Example 32

- 15 6-[2-Amino-4-(4-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(4-pyridinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

IR (KBr): 3295, 1658, 1585, 1411, 1236 cm⁻¹

- 20 NMR (DMSO-d₆, δ): 6.77(1H, d, J=9.8 Hz), 7.11(1H, d, J=9.8 Hz), 7.21(2H, s), 7.33-7.36(2H, m), 8.47(1H, s), 8.60-8.63(2H, m), 13.0(1H, s)

ESI/MS: 265 [M-H]⁻

Example 33

- 25 6-[2-Amino-4-(1,3-thiazol-2-yl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(1,3-thiazol-2-yl)-2-pyrimidinamine according to a similar manner to that of Example 27.

IR (KBr): 3324, 1633, 1531, 1442, 1228 cm⁻¹

- 30 NMR (DMSO-d₆, δ): 6.75(1H, d, J=9.8 Hz), 7.22(2H, s), 7.34(1H, d, J=9.8 Hz), 7.89-8.04(2H, m), 8.38(1H, s), 13.3(1H, s)

ESI/MS: 273 [M+H]⁺, 295 [M+Na]⁺

Example 34

6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(2-furyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 262-268°C (water)

IR (KBr): 3342, 1629, 1573, 1471, 1224 cm⁻¹

NMR (DMSO-d₆, δ): 6.61-6.64 (1H, m), 6.82-6.93 (2H, m), 7.01 (2H, s), 7.26 (1H, d, J=9.8 Hz), 7.78 (1H, s), 8.28 (1H, s), 13.1 (1H, s)

ESI/MS: 278 [M+Na]⁺

Example 35

6-[2-Amino-4-(4-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(4-methylphenyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 249°C (water)

IR (KBr): 3154, 1641, 1583, 1481, 1226 cm⁻¹

NMR (DMSO-d₆, δ): 2.32 (3H, s), 6.68 (1H, d, J=9.8 Hz), 6.88 (1H, d, J=9.8 Hz), 7.03 (2H, s), 7.20 (2H, d, J=8.0 Hz), 7.30 (2H, d, J=8.0 Hz), 8.37 (1H, s), 13.1 (1H, s)

ESI/MS: 280 [M+H]⁺, 302 [M+Na]⁺

Example 36

6-[2-Amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3,4-difluorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 307°C (water)

IR (KBr): 3334, 1681, 1589, 1482, 1232 cm⁻¹

NMR (DMSO-d₆, δ): 6.75 (1H, d, J=9.8 Hz), 7.03 (1H, d, J=9.8 Hz), 7.14-7.19 (2H, m), 7.40-7.94 (3H, m), 8.43 (1H, s), 13.1 (1H, s)

ESI/MS: 301 [M+H]⁺, 323 [M+Na]⁺

Example 37

6-[2-Amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3,4-dimethoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 225°C (water)

IR (KBr): 3174, 1644, 1587, 1425, 1265 cm⁻¹

NMR (DMSO-d₆, δ): 3.68(3H, s), 3.77(3H, s), 6.70(1H, d, J=9.8 Hz), 6.86-7.10(6H, m), 8.34(1H, s), 13.1(1H, s)

ESI/MS: 326 [M+H]⁺, 348 [M+Na]⁺

Example 38

6-[2-Amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3,4-dichlorophenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 300°C (water)

IR (KBr): 3321, 1681, 1583, 1475, 1226 cm⁻¹

NMR (DMSO-d₆, δ): 6.78(1H, d, J=9.8 Hz), 7.11(1H, d, J=9.8 Hz), 7.17(2H, brs), 7.26(1H, d, J=8.4 Hz), 7.69(1H, d, J=8.4 Hz), 7.71(1H, d, J=2.0 Hz), 8.43(1H, s), 13.1(1H, s)

ESI/MS: 356, 358 and 360 [M+Na]⁺

Example 39

6-[2-Amino-4-(2-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(2-methylphenyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 313°C (water)

IR (KBr): 3378, 1643, 1581, 1490, 1234 cm⁻¹

NMR (DMSO-d₆, δ): 2.06(3H, s), 6.57(1H, d, J=9.8 Hz), 6.72(1H, d, J=9.8 Hz), 7.08-7.32(4H, m), 8.44(1H, s), 13.04(1H, s)

ESI/MS: 302 [M+Na]⁺

Example 40

6-[2-Amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(2-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

5 mp: 273°C (water)

IR (KBr): 3365, 1646, 1575, 1490, 1228 cm^{-1}

NMR (DMSO- d_6 , δ): 3.57(3H, s), 6.66(1H, d, $J=9.8$ Hz), 6.91(1H, d, $J=9.8$ Hz), 7.00(2H, s), 6.98-7.07(2H, m), 7.36-7.45(2H, m), 8.35(1H, s), 12.09(1H, s)

10 ESI/MS: 318 $[\text{M}+\text{Na}]^+$

Example 41

6-[2-Amino-4-(2-thienyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(2-thienyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

15 to that of Example 27.

mp: 265°C (water)

IR(KBr): 3330, 1654, 1523, 1430, 1213 cm^{-1}

NMR (DMSO- d_6 , δ): 6.87(1H, d, $J=9.8$ Hz), 7.00-7.10(2H, m), 7.01(2H, s), 7.26(1H, d, $J=9.8$ Hz), 7.73(1H, s), 8.28(1H, s), 13.1(1H, s)

20 s)

ESI/MS: 294 $[\text{M}+\text{Na}]^+$

Example 42

6-[2-Amino-4-(3-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 5-(6-methoxy-3-pyridazinyl)-4-(3-methylphenyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

25 to that of Example 27.

mp : 216°C (water)

IR (KBr): 3403, 1641, 1575, 1442, 1207 cm^{-1}

NMR (DMSO- d_6 , δ): 2.30(3H, s), 6.58(1H, d, $J=9.8$ Hz), 6.86(1H, d, $J=9.8$ Hz), 7.05(2H, s), 7.09-7.40(4H, m), 8.38(1H, s), 13.08(1H, s)

30 s)

ESI/MS: 302 $[\text{M}+\text{Na}]^+$

Example 43

6-[2-Amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared from 4-(3-methoxyphenyl)-5-(6-methoxy-3-pyridazinyl)-2-pyrimidinamine according to a similar manner to that of Example 27.

mp: 134°C (water)

IR (KBr): 3336, 1671, 1575, 1491, 1216 cm⁻¹

NMR (DMSO-d₆, δ): 3.72(3H, s), 6.68(1H, d, J=9.8 Hz), 6.88(1H, d, J=9.8 Hz), 7.02(2H, s), 6.87-7.07(2H, m), 7.26-7.43(2H, m), 8.38(1H, s), 13.1(1H, s)

ESI/MS: 318 [M+Na]⁺

Example 44

6-[2-Amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone (59.0 mg) was dissolved in dimethylformamide (5 ml). To the solution was added potassium t-butoxide (29.2 mg) and isopropyl iodide (44.2 mg). The reaction mixture was stirred at 25°C for 2 hours. The reaction mixture was portioned to ethyl acetate and water. The organic layer was separated and washed with brine. The combined aqueous layer was extracted with ethyl acetate. The combined organic layer was passed to diatomaceous earth column. The organic solution was concentrated under reduced pressure to give a residue. The above residue was purified by column chromatography on silica gel (chloroform (100%) and chloroform-methanol (95:5)). The fraction containing product was concentrated under reduced pressure to give crystal residue. The residue was recrystallized from ethanol-water (4:1) to give

6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (44.0 mg).

mp: 216.5°C (ethanol-water)

IR (KBr): 3477, 1650, 1555, 1481, 1411 cm⁻¹

NMR (DMSO-d₆, δ): 1.14(6H, d, J=6.6 Hz), 3.76(3H, s), 5.02-5.15(1H, m), 6.78(1H, d, J=9.6 Hz), 6.94(2H, d, J=6.8 Hz), 6.98(2H,

s), 7.08 (1H, d, J=9.6 Hz), 7.32 (2H, d, J=6.8 Hz), 8.38 (1H, s)

ESI/MS: 338 [M+H]⁺, 360 [M+Na]⁺

Example 45

5 6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

10 mp: 195°C (ethanol-water)

IR (KBr): 3477, 1658, 1550, 1488, 1411 cm⁻¹

NMR (DMSO-d₆, δ): 1.02 (6H, d, J=6.6 Hz), 4.96-5.10 (1H, m), 6.85 (1H, d, J=9.6 Hz), 7.12 (2H, s), 7.28 (1H, d, J=9.6 Hz), 7.35 (2H, d, J=6.6 Hz), 7.47 (2H, d, J=6.6 Hz), 8.47 (1H, s)

15 ESI/MS: 342 and 344 [M+H]⁺, 364 and 366 [M+Na]⁺

Example 46

 6-[2-Amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 174°C (ethanol-water)

IR (KBr): 3477, 1650, 1555, 1481, 1411 cm⁻¹

20 NMR (DMSO-d₆, δ): 1.11 (6H, d, J=6.6 Hz), 3.84 (3H, s), 5.01-5.15 (1H, m), 6.78 (1H, d, J=9.6 Hz), 6.94 (2H, d, J=6.8 Hz), 6.98 (2H, s), 7.08 (1H, d, J=9.6 Hz), 7.32 (2H, d, J=6.8 Hz), 8.38 (1H, s)

ESI/MS: 356 [M+H]⁺, 378 [M+Na]⁺

Example 47

30 6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 215°C (ethanol-water)

IR(KBr): 3318, 1668, 1646, 1590, 1533 cm⁻¹

NMR (DMSO-d₆, δ): 1.30(6H, d, J=6.8 Hz), 5.09-5.20(1H, m),
6.60-6.62(1H, m), 6.87-6.92(2H, m), 7.03(2H, s), 7.32(1H, d,
5 J=9.6 Hz), 7.60(1H, d, J=1.2 Hz), 8.33(1H, s)
ESI/MS: 298 [M+H]⁺, 320 [M+Na]⁺

Example 48

6-[2-Amino-4-(4-methylphenyl)-5-pyrimidinyl]-2-isopropyl
-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-
10 methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and
isopropyl iodide according to a similar manner to that of Example
44.

mp: 224°C (ethanol-water)

IR (KBr): 3467, 1633, 1567, 1482, 1411 cm⁻¹

15 NMR (DMSO-d₆, δ): 1.10(6H, d, J=6.6 Hz), 2.30(3H, s), 5.03-5.09(1H,
m), 6.80(1H, d, J=9.6 Hz), 7.04(2H, s), 7.09(1H, d, J=9.6 Hz),
7.16-7.27(4H, m), 8.41(1H, s)

ESI/MS: 322 [M+H]⁺, 344 [M+Na]⁺

Example 49

20 6-[2-Amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-2-
isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-
(3,4-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and
isopropyl iodide according to a similar manner to that of Example
44.

25 mp: 208°C (ethanol-water)

IR (KBr): 3405, 1643, 1581, 1515, 1490, 1282 cm⁻¹

NMR (DMSO-d₆, δ): 1.02(6H, d, J=6.6 Hz), 4.97-5.10(1H, m), 6.87(1H,
d, J=9.6 Hz), 7.06(2H, s), 7.34(1H, d, J=9.6 Hz), 7.39-7.53(3H,
m), 8.49(1H, s)

30 ESI/MS: 344 [M+H]⁺, 366 [M+Na]⁺

Example 50

6-[2-Amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-2-

isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

5 mp: 176°C (ethanol-water)

IR(KBr): 3342, 1645, 1581, 1483, 1409 cm⁻¹

NMR (DMSO-d₆, δ): 0.98(6H, d, J=6.6 Hz), 4.96-5.09(1H, m), 6.90(1H, d, J=9.6 Hz), 7.19(2H, s), 7.26(1H, dd, J=2, 8.2 Hz), 7.36(1H, d, J=9.6 Hz), 7.61-7.67(2H, m), 8.51(1H, s)

10 ESI/MS: 376, 378 and 380 [M+H]⁺, 398, 400 and 402 [M+Na]⁺

Example 51

6-[2-Amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 167°C (ethanol-water)

IR(KBr): 3390, 1659, 1639, 1575, 1465, 1265 cm⁻¹

20 NMR (DMSO-d₆, δ): 1.17(6H, d, J=6.6 Hz), 3.63(3H, s), 3.76(3H, s), 5.07-5.17(1H, m), 6.78(1H, d, J=9.6 Hz), 6.88-7.04(6H, m), 8.38(1H, s)

ESI/MS: 368 [M+H]⁺, 390 [M+Na]⁺

Example 52

6-[2-Amino-4-(3-pyridinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 204°C (ethanol-water)

IR (KBr): 3343, 1654, 1589, 1550, 1290 cm⁻¹

30 NMR (DMSO-d₆, δ): 0.94(6H, d, J=6.6 Hz), 4.92-5.06(1H, m), 6.89(1H, d, J=9.6 Hz), 7.17(2H, s), 7.39-7.46(2H, m), 7.71-7.78(1H, m), 8.50-8.58(3H, m)

ESI/MS: 309 [M+H]⁺, 331 [M+Na]⁺

Example 53

6-[2-Amino-4-(4-pyridinyl)-5-pyrimidinyl]-2-isopropyl-
3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-
5 pyridinyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl
iodide according to a similar manner to that of Example 44.
mp: 219°C (ethanol-water)

IR (KBr): 3343, 1662, 1644, 1585, 1482, 1216 cm⁻¹

NMR (DMSO-d₆, δ): 0.88 (6H, d, J=6.6 Hz), 4.91-5.04 (1H, m), 6.90 (1H,
10 d, J=9.6 Hz), 7.21 (2H, s), 7.25-7.31 (2H, m), 7.47 (1H, d, J=9.6
Hz), 8.56-8.61 (3H, m)

ESI/MS: 309 [M+H]⁺, 331 [M+Na]⁺

Example 54

6-[2-Amino-4-(1,3-thiazol-2-yl)-5-pyrimidinyl]-2-
15 isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-
(1,3-thiazol-2-yl)-5-pyrimidinyl]-3(2H)-pyridazinone and
isopropyl iodide according to a similar manner to that of Example
44.

IR (KBr): 3324, 1689, 1633, 1589, 1531, 1228 cm⁻¹

20 NMR (DMSO-d₆, δ): 1.23 (6H, d, J=6.6 Hz), 5.09-5.19 (1H, m), 6.80 (1H,
d, J=9.6 Hz), 7.24 (2H, s), 7.38 (1H, d, J=9.6 Hz), 7.89 (1H,
d, J=3.2 Hz), 7.93 (1H, d, J=3.2 Hz), 8.43 (1H, s)

ESI/MS: 315 [M+H]⁺, 337 [M+Na]⁺

Example 55

25 6-[2-Amino-4-(2-thienyl)-5-pyrimidinyl]-2-isopropyl-
3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-thienyl)-
5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide
according to a similar manner to that of Example 44.
mp: 213°C (ethanol-water)

30 IR (KBr): 3363, 1666, 1646, 1590, 1535, 1482, 1211 cm⁻¹

NMR (DMSO-d₆, δ): 1.24 (6H, d, J=6.6 Hz), 5.11-5.24 (1H, m), 6.92 (1H,
d, J=9.6 Hz), 7.04 (2H, s), 6.96-7.08 (2H, m), 7.32 (1H, d, J=9.6

Hz), 7.71(1H, d, J=5.0 Hz), 8.29(1H, s)

ESI/MS: 314 [M+H]⁺, 336 [M+Na]⁺

Example 56

6-[2-Amino-4-(2-methylphenyl)-5-pyrimidinyl]-2-isopropyl
5 -3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 203°C (ethanol-water)

10 IR (KBr): 3293, 1666, 1627, 1594, 1538, 1486, 1205 cm⁻¹

NMR (DMSO-d₆, δ): 0.96(6H, d, J=6.8 Hz), 2.03(3H, s), 4.90-5.04(1H, m), 6.76(1H, d, J=9.6 Hz), 7.07(2H, s), 7.10-7.29(5H, m), 8.51(1H, s)

ESI/MS: 322 [M+H]⁺, 344 [M+Na]⁺

15 Example 57

6-[2-Amino-4-(3-methylphenyl)-5-pyrimidinyl]-2-isopropyl
-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example
20 44.

mp: 198°C (ethanol-water)

IR(KBr): 3475, 1664, 1624, 1585, 1531, 1482, 1209 cm⁻¹

NMR (DMSO-d₆, δ): 1.06(6H, d, J=6.6 Hz), 2.28(3H, s), 4.98-5.12(1H, m), 6.79(1H, d, J=9.6 Hz), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz),
25 7.21-7.37(4H, m), 8.50(1H, s)

ESI/MS: 322 [M+H]⁺, 344 [M+Na]⁺

Example 58

6-[2-Amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example
30 44.

mp: 170°C (ethanol-water)

IR (KBr): 3330, 1651, 1587, 1535, 1486, 1254 cm^{-1}

NMR (DMSO- d_6 , δ): 0.95 (6H, d, $J=6.6$ Hz), 3.40 (3H, s), 4.90-5.03 (1H, m), 6.79 (1H, d, $J=9.6$ Hz), 6.98 (2H, s), 6.89-7.05 (2H, m), 7.22 (1H, d, $J=9.6$ Hz), 7.31-7.43 (2H, m), 8.39 (1H, s)

5 ESI/MS: 338 $[\text{M}+\text{H}]^+$, 360 $[\text{M}+\text{Na}]^+$

Example 59

6-[2-Amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and isopropyl iodide according to a similar manner to that of Example 44.

mp: 211°C (ethanol-water)

IR(KBr): 3467, 1658, 1623, 1583, 1488, 1288 cm^{-1}

15 NMR (DMSO- d_6 , δ): 1.07 (6H, d, $J=6.6$ Hz), 3.68 (3H, s), 4.99-5.12 (1H, m), 6.80 (1H, d, $J=9.6$ Hz), 6.87-6.98 (3H, m), 7.09 (2H, s), 7.15 (1H, d, $J=9.6$ Hz), 7.25-7.39 (1H, m), 8.50 (1H, s)

ESI/MS: 338 $[\text{M}+\text{H}]^+$, 360 $[\text{M}+\text{Na}]^+$

Example 60

20 6-[2-Amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 259°C (ethanol-water)

25 IR(KBr): 3335, 1685, 1580, 1485, 1411, 1270 cm^{-1}

NMR (DMSO- d_6 , δ): 3.68 (3H, s), 3.78 (3H, s), 6.73 (1H, d, $J=9.6$ Hz), 6.83 (1H, d, $J=9.6$ Hz), 6.95 (2H, d, $J=6.8$ Hz), 6.99 (2H, s), 7.38 (2H, d, $J=6.8$ Hz), 8.35 (1H, s)

ESI/MS: 310 $[\text{M}+\text{H}]^+$, 332 $[\text{M}+\text{Na}]^+$

30 Example 61

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-

chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 264°C (ethanol-water)

IR (KBr): 3330, 1685, 1572, 1480, 1411, 1230 cm^{-1}

- 5 NMR (DMSO- d_6 , δ): 3.65(3H, s), 6.76(1H, d, $J=9.6$ Hz), 6.91(1H, d, $J=9.6$ Hz), 7.14(2H, s), 7.34-7.51(4H, m), 8.43(1H, s)
ESI/MS: 336 and 338 $[\text{M}+\text{H}]^+$

Example 62

- 10 6-[2-Amino-4-(3-fluorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-fluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 212.5°C (ethanol-water)

IR (KBr): 3330, 1666, 1580, 1485, 1411 cm^{-1}

- 15 NMR (DMSO- d_6 , δ): 3.64(3H, s), 6.76(1H, d, $J=9.6$ Hz), 6.93(1H, d, $J=9.6$ Hz), 7.15(2H, s), 7.13-7.45(4H, m), 8.45(1H, s).
ESI/MS: 298 $[\text{M}+\text{H}]^+$, 320 $[\text{M}+\text{Na}]^+$

Example 63

- 20 6-[2-Amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-fluoro-4-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 245°C (ethanol-water)

- 25 IR (KBr): 3326, 1652, 1585, 1481, 1411 cm^{-1}

NMR (DMSO- d_6 , δ): 3.67(3H, s), 3.86(3H, s), 6.77(1H, d, $J=9.6$ Hz), 7.07(2H, s), 7.12-7.38(3H, m), 8.38(1H, s)

ESI/MS: 328 $[\text{M}+\text{H}]^+$, 350 $[\text{M}+\text{Na}]^+$

Example 64

- 30 6-[2-Amino-4-(2-furyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-furyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according

to a similar manner to that of Example 44.

mp: 234°C (ethanol-water)

IR (KBr): 3326, 1658, 1571, 1411 cm⁻¹

NMR (DMSO-d₆, δ): 3.69(3H, s), 6.61-6.64(1H, m), 6.89(1H, d, J=9.6 Hz), 6.92-6.96(1H, m), 7.03(2H, s), 7.27(1H, d, J=9.6 Hz), 7.77-7.79(1H, m), 8.30(1H, s)

ESI/MS: 270 [M+H]⁺, 292 [M+Na]⁺

Example 65

6-[2-Amino-4-(4-methylphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(4-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 230°C (ethanol-water)

IR (KBr): 3326, 1652, 1585, 1481, 1411cm⁻¹

NMR (DMSO-d₆, δ): 2.37(3H, s), 3.67(3H, s), 6.71(1H, d, J=9.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.05(2H, s), 7.20(2H, d, J=8.2 Hz), 7.31(2H, d, J=8.2 Hz), 8.38(1H, s)

ESI/MS: 294 [M+H]⁺, 316 [M+Na]⁺

Example 66

6-[2-Amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

mp: 231°C (ethanol-water)

IR (KBr): 3322, 1641, 1581, 1515, 1488, 1280 cm⁻¹

NMR (DMSO-d₆, δ): 3.64(3H, s), 6.78(1H, d, J=9.6 Hz), 6.98(1H, d, J=9.6 Hz), 7.15-7.19(3H, m), 7.43-7.57(2H, m), 8.45(1H, s)

ESI/MS: 316 [M+H]⁺, 338 [M+Na]⁺

Example 67

6-[2-Amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-2-

methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dimethoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

5 mp: 232°C (ethanol-water)

IR (KBr): 3386, 1629, 1575, 1481, 1263 cm^{-1}

NMR (DMSO- d_6 , δ): 3.69(3H, s), 3.77(3H, s), 6.74(1H, d, $J=9.6$ Hz), 6.83(1H, d, $J=9.6$ Hz), 6.87-7.06(5H, m), 8.36(1H, s)

ESI/MS: 340 $[\text{M}+\text{H}]^+$, 362 $[\text{M}+\text{Na}]^+$

10 Example 68

6-[2-Amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3,4-dichlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

15

mp: 238°C (ethanol-water)

IR (KBr): 3324, 1641, 1583, 1482, 1407 cm^{-1}

NMR (DMSO- d_6 , δ): 3.64(3H, s), 6.81(1H, d, $J=9.6$ Hz), 7.05(1H, d, $J=9.6$ Hz), 7.20(2H, s), 7.23-7.29(1H, m), 7.62-7.76(2H, m), 8.46(1H, s)

20

ESI/MS: 370, 372 and 374 $[\text{M}+\text{Na}]^+$

Example 69

6-[2-Amino-4-(2-thienyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-thienyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

25

mp: 270°C (ethanol-water)

IR (KBr): 3365, 1654, 1589, 1535, 1485, 1430 cm^{-1}

NMR (DMSO- d_6 , δ): 3.71(3H, s), 6.92(1H, d, $J=9.6$ Hz), 7.03(4H, m), 7.29(1H, d, $J=9.6$ Hz), 7.72-7.75(1H, m), 8.27(1H, s)

30

ESI/MS: 286 $[\text{M}+\text{H}]^+$, 308 $[\text{M}+\text{Na}]^+$

Example 70

6-[2-Amino-4-(2-methylphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

5 mp: 229°C (ethanol-water)

IR (KBr): 3307, 1670, 1617, 1592, 1538, 1477, 1267 cm⁻¹

NMR (DMSO-d₆, δ): 2.06(3H, s), 3.56(3H, s), 6.45(1H, d, J=9.6 Hz), 6.78(1H, d, J=9.6 Hz), 7.09(2H, s), 7.12-7.41(4H, m), 8.49(1H, s)

10 ESI/MS: 294 [M+H]⁺, 316 [M+Na]⁺

Example 71

6-[2-Amino-4-(3-methylphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methylphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

15 mp: 214°C (ethanol-water)

IR (KBr): 3413, 1639, 1579, 1531, 1488, 1402 cm⁻¹

NMR (DMSO-d₆, δ): 2.31(3H, s), 3.67(3H, s), 6.70(1H, d, J=9.6 Hz), 6.81(1H, d, J=9.6 Hz), 7.08(1H, s), 7.24-7.41(1H, m),

20 8.41(1H, s)

ESI/MS: 294 [M+H]⁺, 316 [M+Na]⁺

Example 72

6-[2-Amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(2-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.

25 mp: 225°C (ethanol-water)

IR (KBr): 3340, 1652, 1589, 1535, 1488, 1255 cm⁻¹

NMR (DMSO-d₆, δ): 3.44(3H, s), 3.53(3H, s), 6.71(1H, d, J=9.6 Hz), 6.92(1H, d, J=9.6 Hz), 6.93-7.08(2H, m), 7.34-7.45(2H, m), 8.39(1H, s)

30

ESI/MS: 310 [M+H]⁺, 332 [M+Na]⁺

Example 73

6-[2-Amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(3-methoxyphenyl)-5-pyrimidinyl]-3(2H)-pyridazinone and methyl iodide according to a similar manner to that of Example 44.
mp: 195°C (ethanol-water)

IR (KBr): 3365, 1656, 1624, 1569, 1477, 1268 cm⁻¹

NMR (DMSO-d₆, δ): 3.66(3H, s), 3.72(3H, s), 6.72(1H, d, J=9.6 Hz), 6.83(1H, d, J=9.6 Hz), 6.87-7.03(2H, m), 7.10(1H, s), 7.26-7.40(2H, m), 8.41(1H, s)

ESI/MS: 310 [M+H]⁺, 332 [M+Na]⁺

Example 74

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: >250°C (95% EtOH)

NMR (DMSO-d₆, δ): 3.44(3H, s), 6.77(1H, d, J=9.6 Hz), 7.10(1H, d, J=9.6 Hz), 7.18(2H, brd. s), 7.32-7.47(3H, m), 7.62(1H, d, J=7.9 Hz), 8.56(1H, s)

ESI/MS: 380 and 382 [M+Na]⁺

Example 75

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 16.

ESI/MS: 302 [M+Na]⁺

Example 76

6-[2-Amino-4-(2-bromophenyl)-5-pyrimidinyl]-2-(heptadeutero-isopropyl)-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 2.

mp: 203-204°C (95% EtOH)

NMR (CDCl₃, δ): 5.39(2H, brd. s), 6.73(1H, d, J=9.6 Hz), 6.93(1H, d, J=9.6 Hz), 7.22-7.41(3H, m), 7.55(1H, d, J=8.0 Hz), 8.56(1H,

s)

ESI/MS: 415 and 417 $[M+Na]^+$

Example 77

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-(heptadeuteroisopropyl)-3(2H)-pyridazinone was obtained according to a similar manner to that of Example 16.
mp: 214-215°C (95% EtOH)
NMR (DMSO- d_6 , δ): 6.80(1H, d, $J=9.6$ Hz), 7.18(1H, d, $J=9.6$ Hz), 7.30-7.41(5H, m), 8.46(1H, s)

ESI/MS: 373 $[M+Na]^+$

Example 78

A solution of 6-[1-benzoyl-2,2-bis(methylthio)vinyl]-2-isopropyl-3(2H)-pyridazinone (4.00 g) and guanidine carbonate (1.00 g) in N,N-dimethylacetamide (4 ml) was stirred at 130-135°C for 2 hours. After addition of guanidine carbonate (1.00 g), the mixture was stirred at the same temperature for 8 hours and poured into water (80 ml) to give a precipitate. The precipitate was collected by filtration, dissolved in chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was dissolved in acetone under reflux and diisopropyl ether was added to the solution to give 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.26 g).

mp: 221-222°C (chloroform - diisopropyl ether)

IR (KBr): 3500, 3286, 3151, 1658, 1620, 1587, 1539 cm^{-1}

ESI/MS: 729 $[2M+Na]^+$, 376 $[M+Na]^+$, 354 $[M+H]^+$

1H NMR (CDCl₃, δ): 1.26(6H, d, $J=6.66$ Hz), 2.50(3H, s), 5.20(2H, br.s), 5.29(1H, 7-plet, $J=6.66$ Hz), 6.70(1H, d, $J=9.50$ Hz), 6.82(1H, d, $J=9.50$ Hz), 7.24-7.35(5H, m)

1H NMR (DMSO- d_6 , δ): 1.09(6H, d, $J=6.62$ Hz), 2.47(3H, s), 5.08(1H, 7-plet, $J=6.62$ Hz), 6.78(1H, d, $J=9.52$ Hz), 7.03(2H, br.s), 7.15(1H, d, $J=9.52$ Hz), 7.23-7.35(5H, m)

Elemental Analysis for $C_{18}H_{19}N_5OS$

Calcd.: C, 61.17; H, 5.42; N, 19.81

Found : C, 61.27; H, 5.53; N, 19.71

Example 79

5 Under ice-cooling, 3-chloroperbenzoic acid (70 % purity)
(0.70 g) was added to a solution of
6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (1.01 g) in dichloromethane
(10 ml). After stirring at ambient temperature for 5 hours,
10 the mixture was washed with saturated aqueous sodium thiosulfate,
saturated aqueous sodium hydrogen carbonate and brine,
successively, dried over magnesium sulfate and concentrated
under reduced pressure to give a residue. The residue was purified
by column chromatography on silica gel. With an elution of
15 a mixture of n-hexane and ethyl acetate (30 : 70 v/v) was given
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone as a solid (29 mg). Next, with
an elution of a mixture of methanol and ethyl acetate (2 :
98 v/v) was given 6-[2-amino-4-(methylsulfinyl)-6-phenyl-
20 5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (1.00
g).

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone
25 mp: 225-227°C (dimethyl sulfoxide - acetone)
IR (KBr): 3408, 3302, 3207, 1658, 1630, 1591, 1560, 1512 cm^{-1}
ESI/MS: 761 $[2M+Na]^+$, 392 $[M+Na]^+$
ESI/MS-Neg: 368 $[M-H]^-$
 1H NMR ($CDCl_3$, δ): 1.36 (3H, d, $J=6.60$ Hz), 1.39 (3H, d, $J=6.60$
30 Hz), 2.99 (3H, s), 5.39 (1H, 7-plet, $J=6.60$ Hz), 5.83 (2H, br.s),
6.59 (1H, d, $J=9.56$ Hz), 6.64 (1H, d, $J=9.56$ Hz), 7.31-7.48 (5H,
m)

Elemental Analysis for $C_{18}H_{19}N_5O_2S \cdot 0.2H_2O$

Calcd.: C, 57.96; H, 5.24; N, 18.77

Found : C, 58.18; H, 5.17; N, 18.72

6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-

5 2-isopropyl-3(2H)-pyridazinone

mp: 210-211°C (ethanol)

IR (KBr): 3384, 3203, 1653, 1631, 1587, 1564, 1512 cm⁻¹

ESI/MS-Neg: 384 [M-H]⁻

¹H NMR (CDCl₃, δ): 1.21(6H, d, J=6.62 Hz), 3.28(3H, s), 5.27(1H,
10 7-plet, J=6.62 Hz), 5.54(2H, br.s), 6.74(1H, d, J=9.52 Hz),
6.96(1H, d, J=9.52 Hz), 7.28-7.38(5H, m)

Elemental Analysis for C₁₈H₁₉N₅O₃S · 0.2H₂O

Calcd.: C, 55.57; H, 5.03; N, 18.00

Found : C, 55.73; H, 5.05; N, 17.71

15 Example 80

A mixture of

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-

2-isopropyl-3(2H)-pyridazinone (150 mg) and sodium methoxide

(35 mg) in methanol (0.6 ml) was heated under reflux for 5

20 hours. After concentration of the mixture, a residue was purified
by column chromatography on silica gel (n-hexane - ethyl acetate
20 : 80 v/v) to give 6-(2-amino-4-methoxy-6-phenyl-
5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (107
mg).

25 mp: 230-233°C (ethanol)

IR (KBr): 3519, 3394, 1660, 1606, 1581, 1543 cm⁻¹

ESI/MS: 697 [2M+Na]⁺, 360 [M+Na]⁺, 338 [M+H]⁺

¹H NMR (CDCl₃, δ): 0.92(6H, d, J=6.62 Hz), 3.95(3H, s), 5.11(1H,
7-plet, J=6.62 Hz), 5.22(2H, br.s), 6.84(1H, d, J=9.52 Hz),
30 7.21-7.30(6H, m)

Elemental Analysis for C₁₈H₁₉N₅O₂

Calcd.: C, 64.08; H, 5.68; N, 20.76

Found : C, 64.24; H, 5.64; N, 20.75

Example 81

Sodium hydride (60 % in oil suspension) (19.5 mg) was added in ethanol (0.6 ml) under ice-cooling. After stirring at the ambient temperature for 30 minutes, 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture. The mixture was heated at 100-105°C for 5 hours in a sealed tube. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give 6-(2-amino-4-ethoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (99 mg).

mp: 187.5-188.5°C (ethanol - diisopropyl ether)
IR (KBr): 3521, 3388, 1658, 1608, 1579, 1545 cm⁻¹
ESI/MS: 725[2M+Na]⁺, 374[M+Na]⁺, 352[M+H]⁺
¹H NMR (CDCl₃, δ): 0.94(6H, d, J=6.62 Hz), 1.35(3H, t, J=7.06 Hz), 4.41(2H, q, J=7.06 Hz), 5.05-5.19(3H, m), 6.82(1H, d, J=9.50 Hz), 7.21(1H, d, J=9.50 Hz), 7.22-7.30(5H, m)

Elemental Analysis for C₁₉H₂₁N₅O₂ · 0.1H₂O

Calcd.: C, 64.61; H, 6.05; N, 19.83

Found : C, 64.60; H, 5.93; N, 19.81

Example 82

6-(2-Amino-4-isopropoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-propanol according to a similar manner to that of Example 81.

mp: 176.5-177.5°C (diisopropyl ether)
IR (KBr): 3352, 3307, 3184, 1664, 1647, 1635, 1572, 1545 cm⁻¹
ESI/MS: 753[2M+Na]⁺, 388[M+Na]⁺, 366[M+H]⁺
¹H NMR (CDCl₃, δ): 0.95(6H, d, J=6.72 Hz), 1.32(6H, d, J=6.25

Hz), 5.07-5.19(3H, m), 5.40(1H, 7-plet, J=6.25 Hz), 6.81(1H, d, J=9.52 Hz), 7.17(1H, d, J=9.52 Hz), 9.26(5H, s)

Example 83

- 6-[2-Amino-4-(cyclobutyloxy)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and cyclobutanol according to
a similar manner to that of Example 81.
mp: 161-162.5°C (acetone - n-hexane)
IR (KBr): 3381, 3325, 3155, 1653, 1589, 1572, 1547 cm⁻¹
ESI/MS: 400[M+Na]⁺, 378[M+H]⁺
¹H NMR (CDCl₃, δ): 0.94(6H, d, J=6.60 Hz), 1.62-1.85(2H, m),
2.02-2.18(2H, m), 2.39-2.50(2H, m), 5.05-5.33(4H, m), 6.82(1H,
d, J=9.52 Hz), 7.19-7.30(6H, m)
Elemental Analysis for C₂₁H₂₃N₅O₂
Calcd.: C, 66.83; H, 6.14; N, 18.55
Found : C, 66.98; H, 6.17; N, 18.60

Example 84

- 6-[4-(Allyloxy)-2-amino-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 2-propen-1-ol according
to a similar manner to that of Example 81.
mp: 130.5-132.5°C (diisopropyl ether)
IR (KBr): 3489, 3311, 3192, 1647, 1626, 1576, 1545 cm⁻¹
ESI/MS: 749[2M+Na]⁺, 386[M+Na]⁺, 364[M+H]⁺
¹H NMR (CDCl₃, δ): 0.94(6H, d, J=6.56 Hz), 4.85-4.90(2H, m),
5.06-5.36(5H, m), 5.91-6.10(1H, m), 6.83(1H, d, J=9.52 Hz),
7.23(1H, d, J=9.52 Hz), 7.27(5H, s)

Example 85

Sodium hydride (60 % in oil suspension) (19.5 mg) was added
in 2-propyn-1-ol (0.6 ml) under ice-cooling. After stirring
at the ambient temperature for 30 minutes,

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture.
The mixture was heated at 100-105°C for 5 hours. The mixture
was concentrated under reduced pressure and purified by column
5 chromatography on silica gel (n-hexane - ethyl acetate 50 :
50 v/v) to give 6-[2-amino-4-phenyl-6-(2-propynyloxy)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (101
mg).

mp: 145-146.6°C (acetone - diisopropyl ether)

10 IR (KBr): 3410, 3294, 3176, 2121, 1657, 1637, 1591, 1574, 1545
cm⁻¹

ESI/MS: 745[2M+Na]⁺, 384[M+Na]⁺, 362[M+H]⁺

¹H NMR (CDCl₃, δ): 0.93(6H, d, J=6.60 Hz), 2.49(1H, t, J=2.35
Hz), 5.00(2H, d, J=2.35 Hz), 5.09(1H, 7-plet, J=6.60 Hz), 5.20(2H,
15 br.s), 6.84(1H, d, J=9.52 Hz), 7.24(1H, d, J=9.52 Hz), 7.27(5H,
s)

Elemental Analysis for C₂₀H₁₉N₅O₂ · 0.1H₂O

Calcd.: C, 66.14; H, 5.33; N, 19.28

Found : C, 66.19; H, 5.25; N, 19.19

20 Example 86

6-[2-Amino-4-(2-hydroxyethoxy)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and ethylene glycol according
25 to a similar manner to that of Example 85.

mp: 182-183°C (ethanol)

IR (KBr): 3352, 3178, 1646, 1579, 1546 cm⁻¹

ESI/MS: 757[2M+Na]⁺, 390[M+Na]⁺, 368[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.76(6H, d, J=6.60 Hz), 3.63-3.72(2H, m),
30 4.36(2H, t, J=5.04 Hz), 4.81(1H, t, J=5.22 Hz), 4.87(1H, 7-plet,
J=6.60 Hz), 6.85(1H, d, J=9.54 Hz), 6.95(2H, br.s), 7.16-7.34(5H,
m), 7.55(1H, d, J=9.54 Hz)

Elemental Analysis for $C_{19}H_{21}N_5O_3$

Calcd.: C, 62.11; H, 5.76; N, 19.06

Found : C, 62.19; H, 5.78; N, 18.98

Example 87

- 5 6-[2-Amino-4-(2-methoxyethoxy)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 2-methoxyethanol according
to a similar manner to that of Example 85.
- 10 mp: 128-130°C (ethanol)
IR (KBr): 3475, 3325, 3215, 1647, 1630, 1576, 1547 cm^{-1}
ESI/MS: 785[2M+Na]⁺, 404[M+Na]⁺, 382[M+H]⁺
¹H NMR (CDCl₃, δ): 0.93(6H, d, J=6.60 Hz), 3.37(3H, s),
3.65-3.71(2H, m), 4.48-4.54(2H, m), 5.02-5.19(3H, m), 6.82(1H,
15 d, J=9.52 Hz), 7.24-7.31(6H, m)

Example 88

- 6-{2-Amino-4-[2-(dimethylamino)ethoxy]-6-phenyl-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared
from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
20 2-isopropyl-3(2H)-pyridazinone and 2-(dimethylamino)ethanol
according to a similar manner to that of Example 85.
- mp: 130-131.5°C (acetone - diisopropyl ether)
IR (KBr): 3365, 3172, 1664, 1649, 1589, 1570, 1550 cm^{-1}
ESI/MS: 811[2M+Na]⁺, 417[M+Na]⁺, 395[M+H]⁺
- 25 ¹H NMR (CDCl₃, δ): 0.93(6H, d, J=6.62 Hz), 2.27(6H, s), 2.66(2H,
t, J=5.95 Hz), 4.47(2H, t, J=5.95 Hz), 5.11(1H, 7-plet, J=6.62
Hz), 5.18(2H, br.s), 6.82(1H, d, J=9.52 Hz), 7.24-7.30(6H,
m)

Example 89

- 30 Sodium hydride (60 % in oil suspension) (19.5 mg) was added
to a solution of methyl hydroxyacetate (40.7 ml) in
N,N-dimethylacetamide (0.45 ml) under ice-cooling. After
stirring for 30 minutes, 6-[2-amino-4-(methylsulfinyl)-

6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture and the mixture was heated at 100-105°C for 7 hours. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 40 : 60 v/v) to give methyl
5 { [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate as an amorphous (120 mg).
mp: 150-152.5°C

IR (KBr): 3419, 3386, 3309, 3197, 1761, 1657, 1635, 1591, 1545
10 cm⁻¹

ESI/MS: 813[M+Na]⁺, 418[M+Na]⁺, 396[M+H]⁺

¹H NMR (CDCl₃, δ): 0.89(6H, d, J=6.60 Hz), 3.80(3H, s), 4.94(2H, s), 5.10(1H, 7-plet, J=6.60 Hz), 5.24(2H, br.s), 6.86(1H, d, J=9.52 Hz), 7.27(5H, s), 7.43(1H, d, J=9.52 Hz)

15 Elemental Analysis for C₂₀H₂₁N₅O₄ · 0.3H₂O

Calcd.: C, 59.93; H, 5.43; N, 17.47

Found : C, 60.13; H, 5.39; N, 17.26

Example 90

2-(2-{[2-Amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}-ethyl)-1H-isoindole-1,3(2H)-dione was prepared from
20 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
2-(2-hydroxyethyl)-1H-isoindole-1,3(2H)-dione according to
25 a similar manner to that of Example 89.

mp: 231.5-232.5°C (acetone - diisopropyl ether)

IR (KBr): 3313, 3195, 1774, 1716, 1653, 1622, 1577, 1545 cm⁻¹

ESI/MS: 1015[2M+N]⁺, 519[M+N]⁺, 497[M+H]⁺

¹H NMR (CDCl₃, δ): 0.83(6H, d, J=6.62 Hz), 4.07(2H, t, J=5.35 Hz), 4.66(2H, t, J=5.35 Hz), 4.93-5.10(3H, m), 6.71(1H, d, J=9.50 Hz), 7.18-7.27(6H, m), 7.69-7.84(4H, m)

30 Elemental Analysis for C₂₇H₂₄N₆O₄ · 0.1H₂O

Calcd.: C, 65.08; H, 4.89; N, 16.86

Found : C, 64.98; H, 4.91; N, 16.78

Example 91

Sodium hydride (60 % in oil suspension) (19.5 mg) was added
5 in 1-propanol (0.6 ml) under ice-cooling. After stirring at
the ambient temperature for 30 minutes,
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (156.5 mg) was added to the
mixture. The mixture was heated at 100-105°C for 7 hours in
10 a sealed tube. The mixture was concentrated under reduced pressure
and purified by column chromatography on silica gel (n-hexane
- ethyl acetate 20 : 80 v/v) to give
6-(2-amino-4-phenyl-6-propoxy-5-pyrimidinyl)-2-isopropyl-
3(2H)-pyridazinone as a solid (136 mg).
15 mp: 127.5-129°C (ethanol - diisopropyl ether)
IR (KBr): 3354, 3311, 1662, 1589, 1570, 1547 cm⁻¹
ESI/MS: 388 [M+Na]⁺, 366 [M+H]⁺
¹H NMR (CDCl₃, δ): 0.92-1.00 (9H, m), 1.65-1.83 (2H, m), 4.30 (2H,
t, J=6.55 Hz), 5.05-5.19 (3H, m), 6.82 (1H, d, J=9.52 Hz), 7.21 (1H,
20 d, J=9.52 Hz), 7.26 (5H, s)

Example 92

6-[2-Amino-4-(2-fluoroethoxy)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
25 2-isopropyl-3(2H)-pyridazinone and 2-fluoroethanol according
to a similar manner to that of Example 91.
mp: 129-130.5°C (ethanol - diisopropyl ether)
IR (KBr): 3491, 3327, 3207, 1649, 1635, 1576, 1545 cm⁻¹
ESI/MS: 761 [2M+Na]⁺, 392 [M+Na]⁺, 370 [M+H]⁺
30 ¹H NMR (CDCl₃, δ): 0.93 (6H, d, J=6.60 Hz), 4.54-4.58 (2H, m),
4.66-4.72 (1H, m), 4.79-4.84 (1H, m), 5.06-5.20 (3H, m), 6.83 (1H,
d, J=9.52 Hz), 7.21-7.28 (6H, m)

Example 93

Sodium hydride (60 % in oil suspension) (18.7 mg) was added to a solution of benzyl alcohol (52.4 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture and the mixture was heated at 100-105°C for 7 hours. Water (4.5 ml) was added to the mixture to give a solid. The solid was collected by filtration, dissolved in chloroform (5 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 40 : 60 v/v) to give 6-[2-amino-4-(benzyloxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (124 mg).

mp: 162-163°C (acetone)
IR (KBr): 3357, 3309, 3168, 1651, 1589, 1570, 1545, 1490 cm⁻¹
ESI/MS: 849[2M+Na]⁺, 436[M+Na]⁺, 414[M+H]⁺
¹H NMR (CDCl₃, δ): 0.93(6H, d, J=6.61 Hz), 5.11(1H, 7-plet, J=6.61 Hz), 5.17(2H, s), 5.43(2H, s), 6.79(1H, d, J=9.52 Hz), 7.18(1H, d, J=9.52 Hz), 7.23-7.39(10H, m)

Elemental Analysis for C₂₄H₂₃N₅O₂ · 0.1H₂O
Calcd.: C, 69.41; H, 5.63; N, 16.86
Found : C, 69.26; H, 5.59; N, 16.91

Example 94

Sodium hydride (60 % in oil suspension) (18.7 mg) was added to a solution of 2-pyridinylmethanol (48.8 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture and the mixture was heated at 100-105°C for 7 hours. Water (4.5 ml) was added to the mixture to give a solid. The solid was collected by filtration, dissolved

in chloroform (5 ml), dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give

5 6-[2-amino-4-phenyl-
6-(2-pyridinylmethoxy)-5-pyrimidinyl]-2-isopropyl-3(2H)-
pyridazinone as a solid (51 mg).

mp: 177-178°C (acetone - diisopropyl ether)

IR (KBr): 3491, 3141, 1658, 1631, 1591, 1554 cm⁻¹

10 ESI/MS: 851[2M+Na]⁺, 437[M+Na]⁺, 415[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.81(6H, d, J=6.62 Hz), 4.93(1H, 7-plet, J=6.62 Hz), 5.49(2H, s), 6.86(1H, d, J=9.52 Hz), 7.02(2H, s), 7.21-7.42(7H, m), 7.54(1H, d, J=9.52 Hz), 7.77-7.86(1H, m), 8.54-8.57(1H, m)

15 Example 95

Sodium hydride (60 % in oil suspension) (18.7 mg) was added to a solution of 2-(2-pyridinyl)ethanol (57 ml) in N,N-dimethylacetamide (0.45 ml) under ice-cooling. After stirring for 30 minutes, 6-[2-amino-4-(methylsulfonyl)-
20 6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the mixture and the mixture was heated at 100-105°C for 7 hours. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (methanol - ethyl acetate 1 : 99 v/v) to give 6-{2-Amino-4-phenyl-
25 6-[2-(2-pyridinyl)ethoxy]-5-pyrimidinyl}-2-isopropyl-3(2H)-
pyridazinone was prepared as a syrup (71 mg).

IR (KBr): 3471-3327, 3201, 1651, 1589, 1572, 1545 cm⁻¹

ESI/MS: 879[2M+Na]⁺, 451[M+Na]⁺, 429[M+H]⁺

¹H NMR (CDCl₃, δ): 0.88(6H, d, J=6.62 Hz), 3.20(2H, t, J=6.47
30 Hz), 4.77(2H, t, J=6.47 Hz), 5.02-5.13(3H, m), 6.67(1H, d, J=9.52 Hz), 6.91(1H, d, J=9.52 Hz), 7.11-7.32(7H, m), 7.53-7.62(1H, m), 8.54-8.57(1H, m)

Example 96

6-[2-Amino-4-(cyclohexyloxy)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and cyclohexanol according to
5 a similar manner to that of Example 94.

mp: 173-175°C (diisopropyl ether)

IR (KBr): 3419-3309, 3182, 1653, 1589, 1570, 1545 cm⁻¹

ESI/MS: 833[2M+Na]⁺, 428[M+Na]⁺, 406[M+H]⁺

¹H NMR (CDCl₃, δ): 0.84-1.61(8H, m), 0.94(6H, d, J=6.62 Hz),
10 1.87-1.95(2H, m), 5.05-5.22(4H, m), 6.82(1H, d, J=9.52 Hz),
7.21(1H, d, J=9.52 Hz), 7.23-7.31(5H, m)

Example 97

6-[2-Amino-4-phenyl-6-(tetrahydro-2H-pyran-4-yloxy)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared
15 from 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and tetrahydro-2H-pyran-4-ol
according to a similar manner to that of Example 94.

mp: 207-209°C (ethanol - diisopropyl ether)

IR (KBr): 3373, 3329, 3211, 1670, 1649, 1589, 1572, 1539 cm⁻¹

20 ESI/MS: 837[2M+Na]⁺, 430[M+Na]⁺, 408[M+H]⁺

¹H NMR (CDCl₃, δ): 0.97(6H, d, J=6.60 Hz), 1.65-1.85(2H, m),
1.99-2.09(2H, m), 3.54-3.67(2H, m), 3.79-3.91(2H, m),
5.07-5.21(3H, m), 5.29-5.40(1H, m), 6.82(1H, d, J=9.52 Hz),
7.18(1H, d, J=9.52 Hz), 7.25-7.27(5H, m)

25 Elemental Analysis for C₂₂H₂₅N₅O₃

Calcd.: C, 64.85; H, 6.18; N, 17.19

Found : C, 65.05; H, 6.20; N, 17.20

Example 98

6-(2-Amino-4-phenoxy-6-phenyl-5-pyrimidinyl)-
30 2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and phenol according to a
similar manner to that of Example 94.

mp: 218-221°C (methanol)

IR (KBr): 3394, 3305, 3190, 1666, 1631, 1593, 1572, 1539 cm⁻¹

ESI/MS: 821[2M+Na]⁺, 422[M+Na]⁺, 400[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.83(6H, d, J=6.60 Hz), 4.94(1H, 7-plet, J=6.60 Hz), 6.89(1H, d, J=9.54 Hz), 6.99(2H, br.s), 7.20-7.48(10H, m), 7.68(1H, d, J=9.54 Hz)

Elemental Analysis for C₂₃H₂₁N₅O₂ · 3H₂O

Calcd.: C, 68.23; H, 5.38; N, 17.30

Found : C, 68.09; H, 5.22; N, 17.24

10 Example 99

Potassium tert-butoxide (30 mg) was added to a mixture of methyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate (150 mg) in formamide (1.5 ml) and the mixture was heated at 100-105°C for 3 hours. Water (9 ml) was added to give 2-[[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy]acetamide as a solid (101 mg).

mp: 257-261°C (formamide - water)

IR (KBr): 3475, 3411, 3205, 1678, 1637, 1593, 1545 cm⁻¹

20 ESI/MS: 783[2M+Na]⁺, 403[M+Na]⁺, 381[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.75(6H, d, J=6.61 Hz), 4.77(2H, s), 4.90(1H, 7-plet, J=6.61 Hz), 6.89(1H, d, J=9.56 Hz), 6.96(2H, s), 7.04-7.39(7H, m), 7.69(1H, d, J=9.56 Hz)

Elemental Analysis for C₁₉H₂₀N₆O₃

25 Calcd.: C, 59.99; H, 5.30; N, 22.09

Found : C, 59.95; H, 5.27; N, 22.06

Example 100

A solution of methyl

30 {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetate (600 mg) in a mixture of 1N aqueous sodium hydroxide (4.5 ml) and tetrahydrofuran (4.5 ml) was heated at 60-65°C for 3 hours. Under ice-cooling, 1N

hydrochloric acid (4.5 ml) was added to the mixture. The mixture was extracted with ethyl acetate, dried over magnesium sulfate and concentrated under reduced pressure to give a residue.

The residue was suspended with acetone to give

- 5 { [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy } acetic acid as a solid (406 mg).

mp: 215-217°C (acetone)

IR (KBr): 1653, 1591, 1576 cm^{-1}

ESI/MS: 404 $[\text{M}+\text{Na}]^+$, 382 $[\text{M}+\text{H}]^+$

- 10 ^1H NMR (DMSO- d_6 , δ): 0.76 (6H, d, $J=6.60$ Hz), 4.83-4.98 (3H, m), 6.90 (1H, d, $J=9.53$ Hz), 7.00 (2H, s), 7.19-7.37 (5H, m), 7.54 (1H, d, $J=9.53$ Hz), 13.2 (1H, br.s)

Example 101

A mixture of

- 15 { [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy } acetic acid (150 mg), methylamine hydrochloride (31.9 mg), 1-hydroxybenzotriazole (63.8 mg), triethylamine (65.8 μl) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (90.5 mg) in

- 20 dimethylformamide (0.9 ml) was stirred at ambient temperature for 70 hours. The mixture was concentrated under reduced pressure to give a residue. The residue was added to a mixture of water and ethyl acetate. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure and purified
25 by column chromatography on silica gel (methanol - ethyl acetate 2 : 98 v/v) to give 2-{ [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy }-N-methylacetamide as a solid (142 mg).

mp: 204-205.5°C (ethanol - diisopropyl ether)

- 30 IR (KBr): 3440, 3307, 3168, 1680, 1658, 1595, 1539 cm^{-1}

ESI/MS-Neg: 393 $[\text{M}-\text{H}]^-$

^1H NMR (CDCl_3 , δ): 1.00 (6H, d, $J=6.62$ Hz), 2.87 (3H, d, $J=4.94$

Hz), 4.89(2H, s), 5.15-5.31(3H, m), 6.10(1H, br.s), 6.81(1H, d, J=9.50 Hz), 7.04(1H, d, J=9.50 Hz), 7.26-7.35(5H, m)

Elemental Analysis for C₂₀H₂₂N₆O₃

Calcd.: C, 60.90; H, 5.62; N, 21.31

5 Found : C, 60.82; H, 5.64; N, 21.22

Example 102

2-([2-Amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy)-

10 N,N-dimethylacetamide was prepared from {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetic acid and N,N-dimethylamine hydrochloride according to a similar manner to that of Example 101.

mp: 133-135.5°C (acetone - hexane)

15 IR (KBr): 3462, 3309, 3192, 1657, 1591, 5174, 1545 cm⁻¹

ESI/MS: 839[2M+Na]⁺, 431[M+Na]⁺, 409[M+H]⁺

¹H NMR (CDCl₃, δ): 0.87(6H, d, J=6.62 Hz), 3.01(3H, s, J=3.01 Hz), 3.04(3H, s, J=3.04 Hz), 5.00-5.14(5H, m), 6.86(1H, d, J=9.52 Hz), 7.21-7.30(5H, m), 7.67(1H, d, J=9.52 Hz)

20 Example 103

2-([2-Amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy)-

N-cyclopropylacetamide was prepared from {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy}acetic acid and cyclopropylamine according to a similar manner to that of Example 101.

mp: 87-92°C (amorphous)

IR (KBr): 3316, 1651, 1589, 1576, 1541 cm⁻¹

ESI/MS: 863[2M+Na]⁺, 443[M+Na]⁺, 421[M+H]⁺

30 ¹H NMR (CDCl₃, δ): 0.41-0.50(2H, m), 0.75-0.90(2H, m), 1.06(6H, d, J=6.60 Hz), 2.64-2.75(1H, m), 4.84(2H, s), 5.21(1H, 7-plet, J=6.60 Hz), 5.29(2H, s), 6.15(1H, br.s), 6.82(1H, d, J=9.52 Hz), 7.09(1H, d, J=9.52 Hz), 7.26-7.34(5H, m)

Example 104

A solution of

2-(2-([2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]oxy)ethyl)-

- 5 1H-isoindole-1,3(2H)-dione (225 mg) and hydrazine hydrate (0.5 ml) in ethanol (4.5 ml) was heated under reflux for 3 hours. The precipitate was filtered off and the mother liquid was concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel
10 (Chromatorex NH) (methanol - ethyl acetate 1: 99 v/v) to give 6-[2-amino-4-(2-aminoethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (108 mg).

mp: 213-216°C (acetone)

IR (KBr): 3431, 3352, 3248, 1666, 1647, 1564 cm⁻¹

- 15 ESI/MS: 755[2M+Na]⁺, 389[M+Na]⁺, 367[M+H]⁺

¹H NMR (CDCl₃, δ): 1.41(6H, d, J=6.62 Hz), 3.60-3.72(2H, m), 3.78-3.87(2H, m), 5.05(2H, br.s), 5.35(1H, 7-plet, J=6.62 Hz), 6.47(1H, d, J=9.60 Hz), 6.50(1H, d, J=9.60 Hz), 7.26-7.42(7H, m)

- 20 Elemental Analysis for C₁₉H₂₂N₆O₂ · 0.4H₂O

Calcd.: C, 61.08; H, 6.15; N, 22.49

Found : C, 61.21; H, 6.23; N, 22.32

Example 105

In a sealed tube, a mixture of

- 25 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (200 mg) in 2M ammonia solution in methanol (2 ml) was heated at 60-65°C for 90 hours. After cooling at ambient temperature, the precipitate was removed by filtration and the mother liquid was concentrated under
30 reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (methanol - ethyl acetate 3 : 97 v/v) to give 6-(2,4-diamino-6-phenyl-5-pyrimidinyl)-

2-isopropyl-3(2H)-pyridazinone as a solid (20 mg).

mp: 258-260°C (ethanol suspension)

IR (KBr): 3417, 3363, 1645, 1610, 1576, 1552 cm⁻¹

ESI/MS: 345[M+Na]⁺, 323[M+H]⁺

- 5 ¹H NMR (DMSO-d₆, δ): 1.01(6H, d, J=6.60 Hz), 5.05(1H, 7-plet, J=6.60 Hz), 6.27(2H, br.s), 6.34(2H, br.s), 6.68(1H, d, J=9.50 Hz), 6.93(1H, d, J=9.50 Hz), 7.18-7.30(5H, m)

Example 106

- 6-[2-Amino-4-(methylamino)-6-phenyl-5-pyrimidinyl]-
10 2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 40 % methylamine solution
in methanol according to a similar manner to that of Example
105.

- 15 mp: 268-270°C (methanol)

IR (KBr): 3357, 3165, 1657, 1587, 1564 cm⁻¹

ESI/MS: 695[2M+Na]⁺, 359[M+Na]⁺, 337[M+H]⁺

- ¹H NMR (DMSO-d₆, δ): 1.09(6H, d, J=6.61 Hz), 2.80(3H, d, J=4.60 Hz), 5.04(1H, 7-plet, J=6.61 Hz), 6.34(2H, br.s), 6.47(1H,
20 q, J=4.60 Hz), 6.71(1H, d, J=9.50 Hz), 6.99(1H, d, J=9.50 Hz),
7.16-7.28(5H, m)

Elemental Analysis for C₁₈H₂₀N₆O

Calcd.: C, 64.27; H, 5.99; N, 24.98

Found : C, 64.21; H, 6.00; N, 24.85

- 25 Example 107

- 6-[2-Amino-4-(dimethylamino)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 2M dimethylamine solution
30 in tetrahydrofuran according to a similar manner to that of
Example 105.

mp: 293-296°C (tetrahydrofuran)

IR (KBr): 3494, 3275, 3136, 1658, 1622, 1587, 1558 cm⁻¹

ESI/MS: 723[2M+Na]⁺, 373[M+Na]⁺, 351[M+H]⁺

¹H NMR (DMSO-d₆, δ): 1.01 (6H, d, J=6.60 Hz), 2.78 (6H, s), 5.03 (1H, 7-plet, J=6.60 Hz), 6.39 (2H, br.s), 6.70 (1H, d, J=9.50 Hz), 7.05-7.26 (6H, m)

5 Elemental Analysis for C₁₉H₂₂N₆O

Calcd.: C, 65.12; H, 6.33; N, 23.98

Found : C, 65.07; H, 6.39; N, 23.93

Example 108

6-[2-Amino-4-(ethylamino)-6-phenyl-5-pyrimidinyl]-
10 2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 2M ethylamine solution in
tetrahydrofuran according to a similar manner to that of Example
105.

15 mp: 208-209°C (ethanol - diisopropyl ether)

IR (KBr): 3354, 3305, 3180, 1657, 1635, 1587, 1560 cm⁻¹

ESI/MS: 373[M+Na]⁺, 351[M+H]⁺

¹H NMR (CDCl₃, δ): 1.25 (3H, t, J=5.49 Hz), 1.43 (6H, d, J=6.62
Hz), 3.43-3.57 (2H, m), 4.98 (2H, br.s), 5.38 (1H, 7-plet, J=6.62
20 Hz), 6.46 (1H, d, J=9.91 Hz), 6.48 (1H, d, J=9.91 Hz), 6.83 (1H,
br.s), 7.26-7.41 (5H, m)

Elemental Analysis for C₁₉H₂₂N₆O

Calcd.: C, 65.12; H, 6.33; N, 23.98

Found : C, 64.94; H, 6.44; N, 23.73

25 Example 109

6-[2-Amino-4-phenyl-6-(propylamino)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and propylamine according to
30 a similar manner to that of Example 105.

mp: 209-212°C (propylamine)

IR (KBr): 3344, 3305, 3134, 1655, 1624, 1587, 1566 cm⁻¹

ESI/MS: 751[2M+Na]⁺, 387[M+Na]⁺, 365[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.88 (3H, t, J=7.35 Hz), 1.16 (6H, d, J=6.60 Hz), 1.42-1.61 (2H, m), 3.24-3.34 (2H, m), 5.08 (1H, 7-plet, J=6.60 Hz), 6.32 (2H, br.s), 6.55 (1H, t, J=5.49 Hz), 6.66 (1H, d, J=9.52 Hz), 6.84 (1H, d, J=9.52 Hz), 7.18-7.30 (5H, m)

5 Elemental Analysis for C₂₀H₂₄N₆O · 0.1H₂O :

Calcd.: C, 65.59; H, 6.66; N, 22.95

Found : C, 65.57; H, 6.96; N, 22.97

Example 110

6-[2-Amino-4-(isopropylamino)-6-phenyl-5-pyrimidinyl]-
10 2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and isopropylamine according
to a similar manner to that of Example 105.
mp: 234-236°C (methanol)

15 IR (KBr): 3340, 3280, 3144, 1657, 16226, 1587, 1562 cm⁻¹

ESI/MS: 751[M+Na]⁺, 387[M+Na]⁺, 365[M+H]⁺

¹H NMR (DMSO-d₆, δ): 1.14 (6H, d, J=6.50 Hz), 1.22 (6H, d, J=6.60 Hz), 4.26-4.36 (1H, m), 5.12 (1H, 7-plet, J=6.60 Hz), 6.35 (2H, br.s), 6.41 (1H, d, J=7.78 Hz), 6.60 (1H, d, J=9.56 Hz), 6.72 (1H,
20 d, J=9.56 Hz), 7.19-7.32 (5H, m)

Elemental Analysis for C₂₀H₂₄N₆O

Calcd.: C, 65.91; H, 6.64; N, 23.06

Found : C, 65.83; H, 6.90; N, 22.97

Example 111

25 6-[4-(Allylamino)-2-amino-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and allylamine according to
a similar manner to that of Example 105.

30 mp: 191.5-192.5°C (ethanol - diisopropyl ether)

IR (KBr): 3345, 3180, 1668, 1649, 1595, 1570, 1547 cm⁻¹

ESI/MS: 385[M+Na]⁺, 363[M+H]⁺

^1H NMR (CDCl_3 , δ): 1.39(6H, d, $J=6.68$ Hz), 4.09-4.16(2H, m), 5.01(2H, br.s), 5.15-5.40(3H, m), 5.85-6.10(1H, m), 6.48(2H, s), 6.95(1H, br.s), 7.26-7.41(5H, m)

Elemental Analysis for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}$

5 Calcd.: C, 66.28; H, 6.12; N, 23.19

Found : C, 66.11; H, 6.26; N, 23.13

Example 112

6-[2-Amino-4-(cyclopropylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and cyclopropylamine according to a similar manner to that of Example 105.

mp: 237-239°C (methanol)

IR (KBr): 3325, 3155, 1655, 1624, 1587, 1562 cm^{-1}

15 ESI/MS: 747 $[\text{M}+\text{Na}]^+$, 385 $[\text{M}+\text{Na}]^+$, 363 $[\text{M}+\text{H}]^+$

^1H NMR ($\text{DMSO}-d_6$, δ): 0.42-0.51(2H, m), 0.63-0.73(2H, m), 1.12(6H, d, $J=6.60$ Hz), 2.78-2.91(1H, m), 5.06(1H, 7-plet, $J=6.60$ Hz), 6.39(2H, br.s), 6.60-6.66(2H, m), 6.82(1H, d, $J=9.52$ Hz), 7.16-7.30(5H, m)

20 Elemental Analysis for $\text{C}_{20}\text{H}_{22}\text{N}_6\text{O}$

Calcd.: C, 66.28; H, 6.12; N, 23.19

Found : C, 66.39; H, 6.25; N, 23.13

Example 113

6-[2-Amino-4-(tert-butylamino)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and tert-butylamine according to a similar manner to that of Example 105.

mp: 202-204°C (ethanol - diisopropyl ether)

30 IR (KBr): 3502, 3284, 3120, 1668, 1630, 1593, 1566 cm^{-1}

ESI/MS: 401 $[\text{M}+\text{Na}]^+$, 379 $[\text{M}+\text{H}]^+$

^1H NMR (CDCl_3 , δ): 1.42(6H, d, $J=6.62$ Hz), 1.49(9H, s), 4.88(2H,

br.s), 5.36(1H, 7-plet, J=6.62 Hz), 6.46(2H, s), 6.58(1H, br.s),
7.26-7.37(5H, m)

Elemental Analysis for $C_{21}H_{26}N_6O$

Calcd.: C, 66.64; H, 6.92; N, 22.20

5 Found : C, 66.88; H, 7.10; N, 22.21

Example 114

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) in
2-aminoethanol (2 ml) was heated at 100-105°C for 10 hours.
10 The mixture was concentrated under reduced pressure to give
a residue. The residue was crystallized from ethanol to give
6-{2-amino-4-[(2-hydroxyethyl)amino]-6-phenyl-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone as a solid (96
mg).

15 mp: 221.5-223.5°C (ethanol)

IR (KBr): 3431, 3352, 3248, 1666, 1647, 1564 cm^{-1}

ESI/MS: 389[M+Na]⁺, 367[M+H]⁺

¹H NMR (CDCl₃, δ): 1.69(6H, d, J=6.60 Hz), 3.35-3.51(4H, m),
4.73(1H, br.s), 5.08(1H, 7-plet, J=6.60 Hz), 6.38(2H, br.s),
20 6.64(1H, d, J=9.54 Hz), 6.79(1H, t, J=5.28 Hz), 6.82(1H, d,
J=9.54 Hz), 7.20-7.32(5H, m)

Elemental Analysis for $C_{19}H_{22}N_6O_2 \cdot 0.5H_2O$

Calcd.: C, 60.79; H, 6.17; N, 22.39

Found : C, 60.60; H, 6.31; N, 22.21

25 Example 115

In a sealed tube, a mixture of
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (150mg) in 2-methoxyethylamine
(2 ml) was heated at 100-105°C for 10 hours. The mixture was
30 concentrated under reduced pressure to give a residue. The
residue was crystallized from a mixture of ethanol and diisopropyl
ether to give 6-{2-amino-4-[(2-methoxyethyl)amino]-6-

phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone as a solid (88 mg).

mp: 168-170°C (ethanol - diisopropyl ether)

IR (KBr): 3357, 3172, 1662, 1639, 1589, 1558 cm⁻¹

5 ESI/MS: 783[2M+Na]⁺, 403[M+Na]⁺, 381[M+H]⁺

¹H NMR (CDCl₃, δ): 1.43(6H, d, J=6.64 Hz), 3.36(3H, s), 3.56(2H, t, J=4.78 Hz), 3.65-3.74(2H, m), 4.98(2H, br.s), 5.36(1H, 7-plet, J=6.64 Hz), 6.45(1H, d, J=9.93 Hz), 6.49(1H, d, J=9.63 Hz), 7.12(1H, t, J=4.98 Hz), 7.26-7.40(5H, m)

10 Elemental Analysis for C₂₀H₂₄N₆O₂

Calcd.: C, 63.14; H, 6.36; N, 22.09

Found : C, 63.28; H, 6.56; N, 21.87

Example 116

6-{2-Amino-4-[(2-aminoethyl)amino]-6-phenyl-
15 5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and ethylenediamine according to a similar manner to that of Example 114.

20 mp: 194-197°C (diisopropyl ether)

IR (KBr): 3345, 3172, 1653, 1585, 1558 cm⁻¹

ESI/MS: 388[M+Na]⁺, 366[M+H]⁺

¹H NMR (CDCl₃, δ): 1.43(6H, d, J=6.61 Hz), 1.4-1.7(2H, m), 2.94(2H, t, J=6.03 Hz), 3.50-3.65(2H, m), 4.97(2H, br.s), 5.36(1H, 7-plet, J=6.61 Hz), 6.49(2H, s), 7.07(1H, t, J=5.08 Hz), 7.26-7.39(5H, m)
25

Example 117

6-(2-Amino-4-{[2-(dimethylamino)ethyl]amino}-6-phenyl
-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared
30 from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and N,N-dimethylethylenediamine according to a similar manner to that of Example 115.

mp: 164-165.5°C (ethanol - diisopropyl ether)

IR (KBr): 3375, 3321, 3211, 1666, 1641, 1593, 1547 cm⁻¹

ESI/MS: 809[2M+Na]⁺, 416[M+Na]⁺, 394[M+H]⁺

¹H NMR (CDCl₃, δ): 1.44(6H, d, J=6.63 Hz), 2.20(6H, s), 2.49(2H, t, J=5.99 Hz), 3.49-3.59(2H, m), 5.05(2H, br.s), 5.33(1H, 7-plet, J=6.63 Hz), 6.48(2H, s), 6.99(1H, t, J=4.34 Hz), 7.25-7.38(5H, m)

Elemental Analysis for C₂₁H₂₇N₇O

Calcd.: C, 64.10; H, 6.92; N, 24.92

10 Found : C, 64.13; H, 7.02; N, 24.91

Example 118

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg), 2-aminoacetamide hydrochloride (89.8 mg) and N-ethyl-N,N-diisopropylamine (0.141 ml) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was crystallized from a mixture of ethanol and diisopropyl ether to give 2-[[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]amino]acetamide as a solid (77 mg).

mp: 235-237.5°C (ethanol - diisopropyl ether)

IR (KBr): 3338, 3207, 16535, 1585, 1558 cm⁻¹

ESI/MS: 781[2M+Na]⁺, 402[M+Na]⁺, 380[M+H]⁺

¹H NMR (DMSO-d₆, δ): 1.17(6H, d, J=6.61 Hz), 3.90(2H, d, J=5.00 Hz), 5.06(1H, 7-plet, J=6.61 Hz), 6.41(2H, br.s), 6.68(1H, d, J=9.54 Hz), 6.84(1H, t, J=5.00 Hz), 6.96(1H, d, J=9.54 Hz), 7.13(1H, br.s), 7.20-7.32(5H, m), 7.38(1H, br.s)

Elemental Analysis for C₁₉H₂₁N₇O₂ · 0.3H₂O

Calcd.: C, 59.30; H, 5.66; N, 25.48

30 Found : C, 59.54; H, 5.60; N, 25.23

Example 119

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-

5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and benzylamine (88.7 μ l) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was crystallized from a mixture of ethanol and diisopropyl ether to give
5 6-[2-amino-4-(benzylamino)-
6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (135 mg).

mp: 163-164.5°C (ethanol - diisopropyl ether)

10 IR (KBr): 3388, 3307, 3257, 3195, 1651, 1628, 1583, 1562 cm^{-1}

ESI/MS: 847[2M+Na]⁺, 835[M+Na]⁺, 813[M+H]⁺

¹H NMR (CDCl₃, δ): 1.11(6H, d, J=6.64 Hz), 4.64(2H, d, J=5.02 Hz), 5.03(2H, br.s), 5.21(1H, 7-plet, J=6.64 Hz), 6.45(2H, s), 7.16(1H, t, J=4.87 Hz), 7.13-7.42(10H, m)

15 Example 120

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and benzylamine (105 μ l) in N,N-dimethylacetamide (0.3 ml) was heated at 100-105°C for 10 hours. Water (3 ml) was added and
20 the mixture was stirred. An aqueous layer was removed by decantation. A residue was dissolved in chloroform, dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (n-hexane - ethyl acetate 40 : 60 v/v) to give

25 6-{2-amino-4-[benzyl(methyl)amino]-
6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone as a solid (126 mg).

mp: 167-168°C (ethanol - diisopropyl ether)

IR (KBr): 3496, 3273, 3118, 1657, 1622, 1589, 1554, 1531 cm^{-1}

30 ESI/MS: 449[M+Na]⁺, 427[M+H]⁺

¹H NMR (CDCl₃, δ): 1.15(6H, d, J=6.60 Hz), 2.67(3H, s), 4.74(2H, s), 4.92(2H, br.s), 5.20(1H, 7-plet, J=6.60 Hz), 6.53(1H, d,

J=9.50 Hz), 6.76(1H, d, J=9.50 Hz), 7.13-7.35(10H, m)

Elemental Analysis for $C_{25}H_{26}N_6O$

Calcd.: C, 70.40; H, 6.14; N, 19.70

Found : C, 70.18; H, 6.19; N, 19.64

5 Example 121

6-(2-Amino-4-phenyl-6-[(2-pyridinylmethyl)amino]-
5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared
from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 2-pyridinylmethylaniline
10 according to a similar manner to that of Example 120.

mp: 196-198°C (ethanol)

IR (KBr): 3475, 3367, 3327, 3165, 1657, 1653, 1626, 1587, 1550,
1518 cm^{-1}

ESI/MS: 436[M+Na]⁺, 414[M+H]⁺

15 ¹H NMR (CDCl₃, δ): 1.40(6H, d, J=6.60 Hz), 4.80(2H, d, J=4.72
Hz), 5.06(2H, br.s), 5.33(1H, 7-plet, J=6.60 Hz), 6.51(2H,
s), 7.15-7.40(7H, m), 7.62-7.70(2H, m), 8.49-8.53(1H, m)

Elemental Analysis for $C_{23}H_{23}N_7O \cdot 0.5H_2O$

Calcd.: C, 65.39; H, 5.73; N, 23.21

20 Found : C, 65.47; H, 5.74; N, 23.24

Example 122

6-(2-Amino-4-phenyl-6-[(3-pyridinylmethyl)amino]-
5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared
from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 3-pyridinylmethylaniline
25 according to a similar manner to that of Example 120.

mp: 215-216.5°C (ethanol - diisopropyl ether)

IR (KBr): 3498, 3344, 3296, 3140, 1657, 1630, 1585, 1554 cm^{-1}

ESI/MS: 436[M+Na]⁺, 414[M+H]⁺

30 ¹H NMR (CDCl₃, δ): 1.19(6H, d, J=6.61 Hz), 4.68(2H, d, J=5.40
Hz), 5.02(2H, br.s), 5.26(1H, 7-plet, J=6.61 Hz), 6.47(2H,
s), 7.25-7.43(7H, m), 7.66-7.73(1H, m), 8.55(1H, dd, J=1.54,

4.77 Hz), 8.64(1H, d, J=2.04 Hz)

Elemental Analysis for $C_{23}H_{23}N_7O$

Calcd.: C, 66.81; H, 5.61; N, 23.71

Found : C, 66.54; H, 5.65; N, 23.47

5 Example 123

6-{2-Amino-4-phenyl-6-[(4-pyridinylmethyl)amino]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 4-pyridinylmethylaniline according to a similar manner to that of Example 120.

mp: 221.5-222.5°C (ethanol - diisopropyl ether)

IR (KBr): 3321, 3195, 1658, 1633, 1587, 1554 cm^{-1}

ESI/MS: 436[M+Na]⁺, 414[M+H]⁺

¹H NMR (CDCl₃, δ): 1.26(6H, d, J=6.62 Hz), 4.71(2H, d, J=5.70 Hz), 4.98(2H, br.s), 5.30(1H, 7-plet, J=6.62 Hz), 6.49(2H, s), 7.26-7.43(8H, m), 8.56-8.60(2H, m)

Elemental Analysis for $C_{23}H_{23}N_7O$

Calcd.: C, 66.81; H, 5.61; N, 23.71

Found : C, 66.76; H, 5.76; N, 23.68

20 Example 124

6-{2-Amino-4-[(2-furylmethyl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 2-furylmethylaniline according to a similar manner to that of Example 120.

mp: 213-214°C (ethanol)

IR (KBr): 3361, 3319, 3199, 1668, 1643, 1591, 1547 cm^{-1}

ESI/MS: 425[M+Na]⁺, 403[M+H]⁺

¹H NMR (CDCl₃, δ): 1.10(6H, d, J=6.60 Hz), 4.54(2H, d, J=5.51 Hz), 5.05(1H, 7-plet, J=6.60 Hz), 6.31-6.41(2H, m), 6.45(2H, br.s), 6.67(1H, d, J=9.53 Hz), 6.87(1H, d, J=9.53 Hz), 7.00(1H, t, J=5.51 Hz), 7.22-7.31(5H, m), 7.55-7.57(1H, m)

Elemental Analysis for $C_{22}H_{22}N_6O_2$

Calcd.: C, 65.66; H, 5.51; N, 20.88

Found : C, 65.43; H, 5.59; N, 20.74

Example 125

6-[2-Amino-4-phenyl-6-(1-pyrrolidinyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and pyrrolidine according to
a similar manner to that of Example 115.

mp: >300°C (ethanol)

IR (KBr): 3500, 3276, 3143, 2966, 1666, 1622, 1589, 1552, 1531
cm⁻¹

ESI/MS: 775[2M+Na]⁺, 399[M+Na]⁺, 377[M+H]⁺

¹H NMR (CDCl₃, δ): 1.10(6H, d, J=6.60 Hz), 1.70-1.77(4H, m),
3.12-3.18(4H, m), 5.07(1H, 7-plet, J=6.60 Hz), 6.28(2H, br.s),
6.63(1H, d, J=9.48 Hz), 7.06-7.25(6H, m)

Elemental Analysis for C₂₁H₂₄N₆O

Calcd.: C, 67.00; H, 6.43; N, 22.32

Found : C, 66.75; H, 6.52; N, 22.19

Example 126

6-[2-Amino-4-phenyl-6-(1-piperidinyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and piperidine according to
a similar manner to that of Example 115.

mp: 221-223°C (ethanol - diisopropyl ether)

IR (KBr): 3498, 3286, 3157, 1658, 1621, 1585, 1550 cm⁻¹

ESI/MS: 413[M+Na]⁺, 391[M+H]⁺

¹H NMR (CDCl₃, δ): 1.02(6H, d, J=6.60 Hz), 1.46-1.53(6H, m),
3.21-3.27(4H, m), 4.98(2H, br.s), 5.16(1H, 7-plet, J=6.60 Hz),
6.79(1H, d, J=9.50 Hz), 7.09(1H, d, J=9.50 Hz), 7.11-7.27(5H,
m)

Elemental Analysis for C₂₂H₂₆N₆O

Calcd.: C, 67.67; H, 6.71; N, 21.52

Found : C, 67.54; H, 6.82; N, 21.43

Example 127

6-[2-Amino-4-(4-morpholinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from

- 5 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and morpholine according to
a similar manner to that of Example 115.

mp: 251-253°C (ethanol)

IR (KBr): 3498, 3276, 3149, 1660, 1621, 1589, 1554, 1539 cm⁻¹

- 10 ESI/MS: 807[2M+Na]⁺, 415[M+Na]⁺, 393[M+H]⁺

¹H NMR (CDCl₃, δ): 1.02(6H, d, J=6.60 Hz), 3.27(4H, t, J=4.69
Hz), 3.63(4H, t, J=4.69 Hz), 5.03(2H, br.s), 5.16(1H, 7-plet,
J=6.60 Hz), 6.80(1H, d, J=9.46 Hz), 7.09(1H, d, J=9.46 Hz),
7.12-7.28(5H, m)

- 15 Elemental Analysis for C₂₁H₂₄N₆O₂

Calcd.: C, 64.27; H, 6.16; N, 21.41

Found : C, 64.03; H, 6.27; N, 21.21

Example 128

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-
20 5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (150 mg) and
piperazine (1.748 g) in N,N-dimethylacetamide (0.3 ml) was
heated at 100-105°C for 10 hours. Water (3 ml) was added to
give a solid. The solid was collected by filtration and purified
by column chromatography on silica gel (methanol - ethyl acetate
25 10 : 90 v/v) to give 6-[2-amino-4-phenyl-6-(1-piperazinyl)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone as a solid (80
mg).

mp: 254-256°C (ethanol - diisopropyl ether)

IR (KBr): 3496, 3285, 3155, 1657, 1620, 1585, 1552, 1527 cm⁻¹

- 30 ESI/MS: 805[2M+Na]⁺, 414[M+Na]⁺, 392[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.92(6H, d, J=6.60 Hz), 2.57-2.63(4H, m),
3.07-3.12(4H, m), 4.97(1H, 7-plet, J=6.60 Hz), 6.54(2H, br.s),
6.80(1H, d, J=9.52 Hz), 7.06-7.14(2H, m), 7.22-7.28(3H, m),

7.30(1H, d, J=9.52 Hz)

Elemental Analysis for $C_{21}H_{25}N_7O \cdot 0.1H_2O$

Calcd.: C, 64.14; H, 6.46; N, 24.93

Found : C, 64.07; H, 6.56; N, 24.66

5 Example 129

6-[2-Amino-4-(4-methyl-1-piperazinyl)-6-phenyl-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared
from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and 1-methylpiperazine
10 according to a similar manner to that of Example 114.

mp: 213-215°C (ethanol - diisopropyl ether)

IR (KBr): 3502, 3288, 3163, 1658, 1622, 1587, 1552, 1539 cm^{-1}

ESI/MS: 833[2M+Na]⁺, 428[M+Na]⁺, 406[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.92(6H, d, J=6.60 Hz), 2.13(3H, s),
15 2.21-2.26(4H, m), 3.14-3.18(4H, m), 4.98(1H, 7-plet, J=6.60
Hz), 6.58(2H, br.s), 6.81(1H, d, J=9.52 Hz), 7.06-7.14(2H,
m), 7.22-7.32(4H, m)

Elemental Analysis for $C_{22}H_{27}N_7O$

Calcd.: C, 65.16; H, 6.71; N, 24.18

20 Found : C, 65.03; H, 6.81; N, 24.10

Example 130

Sodium hydride (60 % in oil suspension) (19.5 mg) was added
to a solution of imidazole (35.9 mg) in N,N-dimethylacetamide
(0.45 ml) under ice-cooling. After stirring for 30 minutes,
25 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (150 mg) was added to the
mixture and the mixture was heated at 100-105°C for 15 hours.
Water (3 ml) was added to give a solid. The solid was collected
by filtration and purified by column chromatography on silica
30 gel (methanol - ethyl acetate 3 : 97 v/v) to give
6-[2-amino-4-(1H-imidazol-1-yl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone as a solid (44 mg).

mp: 255-258°C (ethanol)

IR (KBr): 3440, 3136, 1637, 1589, 1574, 1529 cm⁻¹

ESI/MS: 396[M+Na]⁺, 374[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.95(6H, d, J=6.61 Hz), 4.99(1H, 7-plet, J=6.61 Hz), 6.74(1H, d, J=9.50 Hz), 6.97-7.03(2H, m), 7.13(1H, s), 7.23-7.46(7H, m), 7.76(1H, s)

Example 131

6-[2-Amino-4-phenyl-6-(1H-1,2,4-triazol-1-yl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 1H-1,2,4-triazole according to a similar manner to that of Example 130.

mp: 266-268°C (ethanol)

IR (KBr): 3309, 3165, 1666, 1647, 1595, 1531 cm⁻¹

ESI/MS: 771[2M+Na]⁺, 397[M+Na]⁺, 375[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.88(6H, d, J=6.62 Hz), 4.97(1H, 7-plet, J=6.62 Hz), 6.69(1H, d, J=9.52 Hz), 7.07(1H, d, J=9.52 Hz), 7.24-7.38(5H, m), 7.51(2H, br.d), 8.10(1H, s), 9.13(1H, s)

Elemental Analysis for C₁₉H₁₈N₈O · 0.1H₂O

Calcd.: C, 60.66; H, 4.88; N, 29.79

Found : C, 60.65; H, 4.89; N, 29.59

Example 132

6-[2-Amino-4-(1H-benzimidazol-1-yl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 1H-benzimidazole according to a similar manner to that of Example 130.

mp: 242-244°C (ethanol)

IR (KBr): 3464, 3298, 3167, 3103, 1660, 1591, 1571 cm⁻¹

ESI/MS: 869[2M+Na]⁺, 446[M+Na]⁺, 424[M+H]⁺

¹H NMR (CDCl₃, δ): 0.92(6H, d, J=6.62 Hz), 5.08(1H, 7-plet, J=6.62 Hz), 5.53(2H, br.s), 6.55(1H, d, J=9.54 Hz), 6.60(1H,

d, J=9.54 Hz), 7.19-7.47 (7H, m), 7.45-7.55 (1H, m), 7.78-7.80 (1H, m), 7.99 (1H, s)

Elemental Analysis for $C_{24}H_{21}N_7O$

Calcd.: C, 68.07; H, 5.00; N, 23.15

5 Found : C, 67.77; H, 5.01; N, 23.07

Example 133

A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (185 mg) and benzylamine (91.3 ml) in N,N-dimethylacetamide (0.37 ml) was
10 heated at 100-105°C for 10 hours. Water (3 ml) was added to give a solid. The solid was dissolved in chloroform, dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (ethyl acetate) to give

15 6-(2-amino-4-anilino-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (73 mg).

mp: 240-242°C (ethanol)

IR (KBr): 3375, 3305, 3190, 1668, 1633, 1593, 1570, 1495 cm^{-1}

ESI/MS: 819[2M+Na]⁺, 421[M+Na]⁺, 399[M+H]⁺

20 ¹H NMR (CDCl₃, δ): 1.51 (6H, d, J=6.61 Hz), 5.10 (1H, br.s), 5.43 (1H, 7-plet, J=6.61 Hz), 6.51 (2H, s), 7.10-7.59 (10H, m), 8.94 (1H, br.s)

Elemental Analysis for $C_{23}H_{22}N_6O \cdot 0.1H_2O$

Calcd.: C, 69.02; H, 5.59; N, 21.00

25 Found : C, 69.05; H, 5.69; N, 20.75

Example 134

6-{2-Amino-4-[(4,5-dimethyl-1,3-thiazol-2-yl)amino]-6-phenyl-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone,
30 4,5-dimethyl-1,3-thiazol-2-amine hydrochloride and N-ethyl-N,N-diisopropylamine according to a similar manner

to that of Example 133.

mp: 256-257.5°C (ethanol)

IR (KBr): 3415, 3321, 3155, 1651, 1626, 1576, 1541 cm⁻¹

ESI/MS: 456[M+Na]⁺, 434[M+H]⁺

- 5 ¹H NMR (DMSO-d₆, δ): 1.07 (6H, d, J=6.60 Hz), 2.11 (3H, s), 2.23 (3H, s), 5.05 (1H, 7-plet, J=6.60 Hz), 6.70-6.76 (3H, m), 7.05-7.33 (6H, m), 12.7 (1H, br.s)

Elemental Analysis for C₂₂H₂₃N₇OS

Calcd.: C, 60.95; H, 5.35; N, 22.62

- 10 Found : C, 60.89; H, 5.40; N, 22.49

Example 135

- 6-[2-Amino-4-phenyl-6-(2-pyridinylamino)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared
from 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
15 2-isopropyl-3(2H)-pyridazinone and 2-pyridinylamine according
to a similar manner to that of Example 133.

mp: 163-164°C (acetone - hexane)

IR (KBr): 3491, 3300, 3180, 1668, 1630, 1591, 1545 cm⁻¹

ESI/MS: 821[2M+Na]⁺, 422[M+Na]⁺, 400[M+H]⁺

- 20 ¹H NMR (CDCl₃, δ): 1.55 (6H, d, J=6.60 Hz), 5.14 (2H, br.s), 5.41 (1H, 7-plet, J=6.60 Hz), 6.54 (2H, s), 6.92-7.00 (1H, m), 7.33-7.45 (5H, m), 7.64-7.74 (1H, m), 8.24-8.26 (1H, m), 8.46 (1H, d, J=8.48 Hz), 9.45 (1H, br.s)

Elemental Analysis for C₂₂H₂₁N₇O · 0.2H₂O

- 25 Calcd.: C, 65.56; H, 5.35; N, 24.33

Found : C, 65.66; H, 5.30; N, 24.43

Example 136

- A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (200 mg) and
30 potassium fluoride (95 mg) in dimethylsulfoxide (1 ml) was
heated at 100-105°C for 15 hours. Water (20 ml) was added to
give a solid. The solid was collected by filtration and purified

by column chromatography on silica gel (n-hexane - ethyl acetate 50 : 50 v/v) to give 6-(2-amino-4-fluoro-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (35 mg).

5 mp: 231-232.5°C (ethanol)

IR (KBr): 3396, 3325, 3197, 1647, 1631, 1612, 1581, 1504 cm⁻¹

ESI/MS: 673[2M+Na]⁺, 348[M+Na]⁺, 326[M+H]⁺

¹H NMR (CDCl₃, δ): 1.03(6H, d, J=6.63 Hz), 5.18(1H, 7-plet, J=6.63 Hz), 5.46(2H, br.s), 6.84(1H, d, J=9.52 Hz), 7.09(1H,

10 dd, J=1.90, 9.52 Hz), 7.28-7.37(5H, m)

Elemental Analysis for C₁₇H₁₆FN₅O · 0.2H₂O

Calcd.: C, 62.07; H, 5.02; N, 21.29

Found : C, 62.24; H, 4.92; N, 21.10

Example 137

15 A solution of 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (193 mg) and guanidine carbonate (92 mg) in N,N-dimethylacetamide (0.38 ml) was heated at 100-105°C for 15 hours. Water (3 ml) was added to give a solid. The solid was collected by filtration
20 and dried over phosphorous pentoxide to give

N-[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]guanidine as a solid (136 mg).

mp: 272-274.5°C (N,N-dimethylacetamide - water)

IR (KBr): 3348, 1622, 1564, 1510 cm⁻¹

25 ESI/MS: 751[2M+Na]⁺, 365[M+H]⁺

¹H NMR (DMSO-d₆, δ): 0.69(6H, d, J=6.62 Hz), 4.85(1H, 7-plet, J=6.62 Hz), 6.35(2H, br.s), 6.72(1H, d, J=9.50 Hz), 7.00-7.29(9H, m), 7.55(1H, d, J=9.50 Hz)

Elemental Analysis for C₁₈H₂₀N₈O · 0.5H₂O

30 Calcd.: C, 57.90; H, 5.67; N, 30.01

Found : C, 58.16; H, 5.49; N, 29.82

Example 138

6-[2-Amino-4-phenyl-6-(phenylthio)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and benzenethiol according to
5 a similar manner to that of Example 95.

mp: 214-215°C (ethanol)

IR (KBr): 3444, 3313, 3199, 1670, 1620, 1593, 1539, 1520 cm⁻¹

ESI/MS: 853[2M+Na]⁺, 438[M+Na]⁺, 416[M+H]⁺

¹H NMR (CDCl₃, δ): 1.32 (6H, d, J=6.63 Hz), 5.02 (2H, br.s), 5.33 (1H,
10 7-plet, J=6.63 Hz), 6.72 (1H, d, J=9.50 Hz), 6.86 (1H, d, J=9.50
Hz), 7.29-7.56 (10H, m)

Elemental Analysis for C₂₃H₂₁N₅OS

Calcd.: C, 66.48; H, 5.09; N, 16.85

Found : C, 66.31; H, 5.12; N, 16.83

15 Example 139

To a solution of 6-[2-amino-4-(methylthio)-6-phenyl-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (5.00 g) in
methanol (100 ml) was added a 28 % solution of sodium methoxide
in methanol (13.6 ml) and the mixture was refluxed for 36 hours.
20 After cooling at ambient temperature, a precipitate was collected
by filtration and dried under reduced pressure to give
6-(2-amino-4-methoxy-6-phenyl-5-pyrimidinyl)-2-isopropyl-
3(2H)-pyridazinone as a solid (3.76 g).

mp: 230-233°C (ethanol)

25 IR (KBr): 3519, 3394, 1660, 1606, 1581, 1543 cm⁻¹

ESI/MS: 697[2M+Na]⁺, 360[M+Na]⁺, 338[M+H]⁺

ESI/MS-Neg: 336[M-H]⁻

¹H NMR (CDCl₃, δ): 0.92 (6H, d, J=6.62 Hz), 3.95 (3H, s), 5.11 (1H,
7-plet, J=6.62 Hz), 5.22 (2H, br.s), 6.84 (1H, d, J=9.52 Hz),
30 7.21-7.30 (6H, m)

Elemental Analysis for C₁₈H₁₉N₅O₂

Calcd.: C, 64.08; H, 5.68; N, 20.76

Found : C, 64.24; H, 5.64; N, 20.75

Example 140

- A mixture of 6-[2-amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (535 mg) and urea hydrogen peroxide addition compound (143 mg) in acetic acid (0.8 ml) was heated at 70-75°C for 1 hour. Urea hydrogen peroxide addition compound (143 mg) was added and the mixture was stirred at the same temperature. After 1 hour, urea hydrogen peroxide addition compound (143 mg) was added and the mixture was heated at 70-75°C for 3 hours. Water (12 ml) was added to the mixture. A precipitate was collected by filtration, washed with chloroform and dried under reduced pressure to give 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (298 mg).
mp: 291-295°C (acetic acid - water)
- IR (KBr): 3363, 3126, 1645, 1576, 1500 cm^{-1}
ESI/MS: 669[2M+Na]⁺, 346[M+Na]⁺, 324[M+H]⁺
¹H NMR (DMSO-d₆, δ): 0.72(6H, d, J=6.62 Hz), 4.87(1H, 7-plet, J=6.62 Hz), 6.82(1H, d, J=9.55 Hz), 6.91(2H, br.s), 7.17-7.30(4H, m), 7.47-7.50(2H, m), 11.33(1H, br.s)
- Elemental Analysis for C₁₇H₁₇N₅O₂ · 0.8H₂O
Calcd.: C, 60.45; H, 5.55; N, 20.73
Found : C, 60.35; H, 5.46; N, 20.38

Example 141

- A mixture of 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (300 mg) and potassium thioacetate (111 mg) in N,N-dimethylacetamide (0.6 ml) was heated at 100-105°C for one hour. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel. With an elution of a mixture of n-hexane and ethyl acetate (40 : 60 v/v) was given S-[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]ethanethioate as a

solid (8 mg). Next, with an elution of a mixture of n-hexane and ethyl acetate (20 : 80 v/v) was given 6-(2-amino-4-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (73 mg).

5

S-[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-phenyl-4-pyrimidinyl]ethanethioate

mp: 240°C (ethanol - diisopropyl ether)

ESI/MS: 404[M+Na]⁺, 382[M+H]⁺

10 ¹H NMR (CDCl₃, δ): 0.86(6H, d, J=6.62 Hz), 2.28(3H, s), 5.08(1H, 7-plet, J=6.62 Hz), 6.93(1H, d, J=9.46 Hz), 7.17-7.41(6H, m), 7.60(1H, d, J=9.46 Hz), 9.08(1H, br.s)

6-(2-amino-4-phenyl-6-thioxo-1,6-dihydro-5-pyrimidinyl)-
15 2-isopropyl-3(2H)-pyridazinone

mp: 295-299°C (ethanol suspension)

IR (KBr): 1647, 1558 cm⁻¹

ESI/MS: 701[2M+Na]⁺, 362[M+Na]⁺, 340[M+H]⁺

20 ¹H NMR (DMSO-d₆, δ): 0.74(6H, d, J=6.60 Hz), 4.88(1H, 7-plet, J=6.60 Hz), 6.80(1H, d, J=9.50 Hz), 7.04-7.30(7H, m), 7.62(1H, d, J=9.50 Hz), 12.60(1H, br.s)

Example 142

6-[2-Amino-4-(methylthio)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone was prepared from 6-[1-benzoyl-
25 2,2-bis(methylthio)vinyl]-2-methyl-3(2H)-pyridazinone and
guanidine carbonate according to a similar manner to that of
Example 78.

mp: 233-235°C (chloroform - diisopropyl ether)

IR (KBr): 3406, 3315, 3217, 1647, 1624, 1581, 1537 cm⁻¹

30 ESI/MS: 673[2M+Na]⁺, 348[M+Na]⁺, 326[M+H]⁺

¹H NMR (CDCl₃, δ): 2.49(3H, s), 3.80(3H, s), 5.23(2H, br.s),
6.71(1H, d, J=9.52 Hz), 6.77(1H, d, J=9.52 Hz), 7.26-7.41(5H,

m)

^1H NMR (DMSO- d_6 , δ): 2.45 (3H, s), 3.60 (3H, s), 6.79 (1H, d, $J=9.52$ Hz), 7.03 (2H, br.s), 7.09 (1H, d, $J=9.52$ Hz), 7.34 (5H, s)

Example 143

- 5 6-[2-Amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone and
6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylthio)-6-phenyl-
10 5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone and
3-chloroperbenzoic acid according to a similar manner to that
of Example 79.

- 6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
15 2-methyl-3(2H)-pyridazinone
mp: $>250^\circ\text{C}$ (ethanol suspension)
IR (KBr): 3498, 3294, 1668, 1618, 1593, 1554, 1516 cm^{-1}
ESI/MS-Neg: 340 $[\text{M-H}]^-$
 ^1H NMR (CDCl_3 , δ): 3.04 (3H, s), 3.84 (3H, s), 6.06 (2H, br.s),
20 6.56 (1H, d, $J=9.52$ Hz), 6.65 (1H, d, $J=9.52$ Hz), 7.34-7.52 (5H,
m)
 ^1H NMR (DMSO- d_6 , δ): 2.90 (3H, s), 3.67 (3H, s), 6.72 (1H, d, $J=9.56$
Hz), 6.92 (1H, d, $J=9.56$ Hz), 7.37-7.46 (5H, m), 7.62 (2H, br.s)
- 25 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone
mp: $240-243^\circ\text{C}$ (ethanol suspension)
IR (KBr): 3340, 3305, 3190, 1643, 1566 cm^{-1}
ESI/MS: 737 $[\text{2M+Na}]^+$, 380 $[\text{M+Na}]^+$, 358 $[\text{M+H}]^+$
30 ^1H NMR (CDCl_3 , δ): 3.30 (3H, s), 3.77 (3H, s), 5.60 (2H, br.s),
6.75 (1H, d, $J=9.54$ Hz), 6.89 (1H, d, $J=9.54$ Hz), 7.33-7.44 (5H,
m)

Example 144

6-(2-Amino-4-methoxy-6-phenyl-5-pyrimidinyl)-2-methyl-3(2H)-pyridazinone was prepared from

6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone and sodium methoxide according
to a similar manner to that of Example 80.

mp: 218-220°C (ethanol - diisopropyl ether)

IR (KBr): 3421, 1649, 1577 cm⁻¹

ESI/MS: 332[M+Na]⁺, 310[M+H]⁺

¹H NMR (CDCl₃, δ): 3.61(3H, s), 3.93(3H, s), 5.20(2H, br.s),
6.81(1H, d, J=9.52 Hz), 7.07(1H, d, J=9.52 Hz), 7.26-7.35(5H,
m)

Example 145

6-[2-Amino-4-(benzylamino)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone and benzylamine according to a
similar manner to that of Example 120.

mp: >250°C (ethanol suspension)

IR (KBr): 3489, 3346, 3290, 1658, 1633, 1585, 1560 cm⁻¹

ESI/MS: 407[M+Na]⁺, 385[M+H]⁺

¹H NMR (DMSO-d₆, δ): 3.63(3H, s), 4.58(2H, d, J=6.01 Hz), 6.34(2H,
br.s), 6.66(1H, d, J=9.52 Hz), 6.79(1H, d, J=9.52 Hz),
7.18-7.34(11H, m)

Example 146

6-{2-amino-4-phenyl-6-[(2-pyridinylmethyl)amino]-
5-pyrimidinyl}-2-methyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone and 2-pyridinylmethylamine
according to a similar manner to that of Example 120.

mp: 248-250°C (ethanol suspension)

IR (KBr): 3473, 3278, 1664, 1631, 1589, 1576, 1554 cm⁻¹

ESI/MS: 408[M+Na]⁺, 407[M+H]⁺

^1H NMR (DMSO- d_6 , δ): 3.71 (3H, s), 4.67 (2H, d, $J=5.31$ Hz), 6.41 (2H, br.s), 6.64 (1H, d, $J=9.58$ Hz), 6.75 (1H, d, $J=9.58$ Hz), 7.24-7.85 (7H, m), 7.73-7.85 (2H, m), 8.52-8.55 (1H, m)

Example 147

- 5 6-(2-Amino-4-anilino-6-phenyl-5-pyrimidinyl)-2-methyl-3
(2H)-pyridazinone was prepared from
6-[2-amino-4-(methylsulfinyl)-6-phenyl-5-pyrimidinyl]-
2-methyl-3(2H)-pyridazinone and aniline according to a similar
manner to that of Example 133.
- 10 mp: 252-254°C (ethanol)
IR (KBr): 3384, 3307, 3149, 1662, 1649, 1580, 1549 cm^{-1}
ESI/MS: 393 $[\text{M}+\text{Na}]^+$, 371 $[\text{M}+\text{H}]^+$
 ^1H NMR (CDCl_3 , δ): 3.92 (3H, s), 5.08 (2H, br.s), 6.54 (2H, s),
7.08-7.63 (10H, m), 9.23 (1H, br.s)

15 Example 148

- A mixture of
6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
6-(2-amino-4-(methylthio)-6-[4-(methylthio)phenyl]-
20 5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared
from 6-[1-(4-fluorobenzoyl)-2,2-bis(methylthio)vinyl]-
2-isopropyl-3(2H)-pyridazinone and guanidine carbonate
according to a similar manner to that of Example 78.
- 25 6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 232-234°C (ethanol)
IR (KBr): 3516, 3313, 1658, 1587, 1547 cm^{-1}
ESI/MS: 394 $[\text{M}+\text{Na}]^+$, 372 $[\text{M}+\text{H}]^+$
- 30 ^1H NMR (CDCl_3 , δ): 1.27 (6H, d, $J=6.64$ Hz), 2.49 (3H, s), 5.16 (2H,
br.s), 5.31 (1H, 7-plet, $J=6.64$ Hz), 6.74 (1H, d, $J=9.50$ Hz),
6.83 (1H, d, $J=9.50$ Hz), 6.94-7.03 (2H, m), 7.26-7.37 (2H, m)

Elemental Analysis for $C_{18}H_{18}FN_5O_2S$

Calcd.: C, 58.21; H, 4.88; N, 18.86

Found : C, 58.45; H, 4.95; N, 18.65

- 5 6-{2-amino-4-(methylthio)-6-[4-(methylthio)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone
ESI/MS: 821[2M+Na]⁺, 422[M+Na]⁺, 400[M+H]⁺
¹H NMR (DMSO-d₆, δ): 1.30(6H, d, J=6.60 Hz), 2.46(3H, s), 2.48(3H,
s)

10 Example 149

- A mixture of 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
6-{2-amino-4-methoxy-6-[4-(methylthio)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared
15 from a mixture of
6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
6-{2-amino-4-(methylthio)-6-[4-(methylthio)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and a solution
20 of 28 % sodium methoxide in methanol according to a similar
manner to that of Example 139.

- 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone
25 mp: 207-209°C (acetone)
IR (KBr): 3427, 3323, 3217, 1645, 1624, 1581 cm⁻¹
ESI/MS: 733[2M+Na]⁺, 378[M+Na]⁺, 356[M+H]⁺
¹H NMR (CDCl₃, δ): 0.96(6H, d, J=6.60 Hz), 3.95(3H, s),
5.07-5.21(3H, m), 6.85(1H, d, J=9.52 Hz), 6.92-7.03(2H, m),
30 7.21-7.31(3H, m)

6-{2-amino-4-methoxy-6-[4-(methylthio)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

ESI/MS: 789[2M+Na]⁺, 406[M+Na]⁺, 384[M+H]⁺

¹H NMR (CDCl₃, δ): 2.44(3H, s), 3.94(3H, s)

Example 150

- 5 6-[2-Amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and
6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-
pyridazinone were prepared from a mixture of
6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-
10 2-isopropyl-3(2H)-pyridazinone and
6-{2-amino-4-methoxy-6-[4-(methylthio)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and
3-chloroperbenzoic acid according to a similar manner to that
of Example 79.
- 15 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone
mp: 207-209°C (acetone)
IR (KBr): 3427, 3323, 3217, 1645, 1624, 1581 cm⁻¹
- 20 ESI/MS: 733[2M+Na]⁺, 378[M+Na]⁺, 356[M+H]⁺
¹H NMR (CDCl₃, δ): 0.96(6H, d, J=6.60 Hz), 3.95(3H, s),
5.07-5.21(3H, m), 6.85(1H, d, J=9.52 Hz), 6.92-7.03(2H, m),
7.21-7.31(3H, m)
- 25 6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone
mp: 148-151°C (acetone)
IR (KBr): 1660, 1633, 1587, 1566, 1547 cm⁻¹
ESI/MS: 853[2M+Na]⁺, 438[M+Na]⁺, 416[M+H]⁺
- 30 ¹H NMR (CDCl₃, δ): 0.84(6H, d, J=6.62 Hz), 2.98(3H, s), 3.98(3H,
s), 5.10(1H, 7-plet, J=6.62 Hz), 5.20(2H, br.s), 6.89(1H, d,
J=9.54 Hz), 7.35(1H, d, J=9.54 Hz), 7.47(2H, d), 7.88(2H, d)

¹H NMR (DMSO-d₆, δ): 0.69 (6H, d, J=6.60 Hz), 3.15 (3H, s), 3.90 (3H, s), 4.90 (1H, 7-plet, J=6.60 Hz), 6.91 (1H, d, J=9.54 Hz), 7.12 (2H, br.s), 7.45 (2H, d, J=8.32 Hz), 7.57 (1H, d, J=9.54 Hz), 7.87 (2H, d, J=8.32 Hz)

5 Example 151

Under ice-cooling, 3-perbenzoic acid (70 % purity) (1.33 g) was added to a mixture of 6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and 10 6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (1.47 g, molar ratio 6:4) in dichloromethane (15 ml). After stirring at the same temperature for 2 hours, the mixture was washed with saturated aqueous sodium thiosulfate, saturated aqueous sodium 15 hydrogen carbonate and brine, successively, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified by column chromatography on silica gel (n-hexane - ethyl acetate 10 : 90, ethyl acetate and methanol - ethyl acetate=4:96, 8:92, 10:90 v/v, in turn). Successively, 20 6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (101 mg), 6-[2-amino-4-[4-(methylsulfonyl)-phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (41 mg), 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)- 25 5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (510 mg) and 6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfinyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (54 mg) were isolated as a solid, respectively.

30 6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 232-234°C (ethanol)

IR (KBr): 3516, 3313, 1658, 1587, 1547 cm⁻¹

ESI/MS: 394[M+Na]⁺, 372[M+H]⁺

¹H NMR (CDCl₃, δ): 1.27(6H, d, J=6.64 Hz), 2.49(3H, s), 5.16(2H, br.s), 5.31(1H, 7-plet, J=6.64 Hz), 6.74(1H, d, J=9.50 Hz), 6.83(1H, d, J=9.50 Hz), 6.94-7.03(2H, m), 7.26-7.37(2H, m)

5

6-[2-amino-4-[4-(methylsulfonyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 241-243°C (ethanol suspension)

IR (KBr): 3438, 3330, 3224, 1653, 1630, 1583, 1537 cm⁻¹

10 ESI/MS: 885[2M+Na]⁺, 454[M+Na]⁺, 432[M+H]⁺

¹H NMR (CDCl₃, δ): 1.16(6H, d, J=6.60 Hz), 2.52(3H, s), 3.01(3H, s), 5.17-5.35(3H, m), 6.80(1H, d, J=9.52 Hz), 6.99(1H, d, J=9.52 Hz), 7.52(2H, d, J=8.34 Hz), 7.89(2H, d, J=8.34 Hz)

15 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 238-240°C (chloroform - acetone)

IR (KBr): 3506, 3290, 3180, 1667, 1625, 1597, 1552 cm⁻¹

ESI/MS: 797[2M+Na]⁺, 410[M+Na]⁺, 388[M+H]⁺

20 ¹H NMR (CDCl₃, δ): 1.37(3H, d, J=6.64 Hz), 1.40(3H, d, J=6.64 Hz), 2.98(3H, s), 5.40(1H, 7-plet, J=6.64 Hz), 5.75(2H, br.s), 6.61(1H, d, J=9.54 Hz), 6.70(1H, d, J=9.54 Hz), 7.02-7.13(2H, m), 7.35-7.44(2H, m)

¹H NMR (DMSO-d₆, δ): 1.19(6H, d, J=6.60 Hz), 2.85(3H, s), 5.13(2H, 7-plet), 6.77(1H, d, J=9.53 Hz), 7.09(1H, d, J=9.53 Hz), 7.18-7.41(4H, m), 7.63(2H, br.s)

25

Elemental Analysis for C₁₈H₁₈FN₅O₂

Calcd.: C, 58.21; H, 4.88; N, 18.86

Found : C, 58.45; H, 4.95; N, 18.65

30

6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfinyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

ESI/MS: 454[M+Na]⁺

¹H NMR (CDCl₃, δ): 1.33(3H, d, J=6.61 Hz), 1.38(3H, d, J=6.61 Hz), 2.73(3H, s), 2.98(3H, s), 5.77(2H, br.s), 5.38(1H, 7-plet, J=6.61 Hz), 6.65(1H, d, J=9.56 Hz), 6.70(1H, d, J=9.56 Hz),
5 7.53-7.70(4H, m)

¹H NMR (DMSO-d₆, δ): 1.10(6H, d, J=6.63 Hz), 2.73(3H, s), 2.86(3H, s), 5.10(1H, 7-plet, J=6.63 Hz), 6.78(1H, d, J=9.50 Hz), 7.17(1H, d, J=9.50 Hz), 7.48(2H, d, J=8.34 Hz), 7.63-7.71(4H, m)

Example 152

10 Successively,

6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (410 mg),
6-[2-amino-4-[4-(methylsulfonyl)phenyl]-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (257 mg),
15 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (128 mg),
6-[2-amino-4-[4-(methylsulfinyl)phenyl]-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (405 mg) and
6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfonyl)phenyl]-
20 5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone (248 mg) were
isolated as a solid, respectively, from a mixture of
6-[2-amino-4-(4-fluorophenyl)-6-methoxy-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone and
6-{2-amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-
25 5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and
3-chloroperbenzoic acid (70 % purity) according to a similar
manner to that of Example 151.

6-[2-amino-4-(4-fluorophenyl)-6-(methylthio)-
30 5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 232-234°C (ethanol)

IR (KBr): 3516, 3313, 1658, 1587, 1547 cm⁻¹

ESI/MS: 394[M+Na]⁺, 372[M+H]⁺

^1H NMR (CDCl_3 , δ): 1.27 (6H, d, $J=6.64$ Hz), 2.49 (3H, s), 5.16 (2H, br.s), 5.31 (1H, 7-plet, $J=6.64$ Hz), 6.74 (1H, d, $J=9.50$ Hz), 6.83 (1H, d, $J=9.50$ Hz), 6.94-7.03 (2H, m), 7.26-7.37 (2H, m)

- 5 6-[2-amino-4-[4-(methylsulfonyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 241-243°C (ethanol suspension)

IR (KBr): 3438, 3330, 3224, 1653, 1630, 1583, 1537 cm^{-1}

ESI/MS: 885 $[\text{2M}+\text{Na}]^+$, 454 $[\text{M}+\text{Na}]^+$, 432 $[\text{M}+\text{H}]^+$

- 10 ^1H NMR (CDCl_3 , δ): 1.16 (6H, d, $J=6.60$ Hz), 2.52 (3H, s), 3.01 (3H, s), 5.17-5.35 (3H, m), 6.80 (1H, d, $J=9.52$ Hz), 6.99 (1H, d, $J=9.52$ Hz), 7.52 (2H, d, $J=8.34$ Hz), 7.89 (2H, d, $J=8.34$ Hz)

- 15 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone

mp: 238-240°C (chloroform - acetone)

IR (KBr): 3506, 3290, 3180, 1667, 1625, 1597, 1552 cm^{-1}

ESI/MS: 797 $[\text{2M}+\text{Na}]^+$, 410 $[\text{M}+\text{Na}]^+$, 388 $[\text{M}+\text{H}]^+$

- 20 ^1H NMR (CDCl_3 , δ): 1.37 (3H, d, $J=6.64$ Hz), 1.40 (3H, d, $J=6.64$ Hz), 2.98 (3H, s), 5.40 (1H, 7-plet, $J=6.64$ Hz), 5.75 (2H, br.s), 6.61 (1H, d, $J=9.54$ Hz), 6.70 (1H, d, $J=9.54$ Hz), 7.02-7.13 (2H, m), 7.35-7.44 (2H, m)

^1H NMR ($\text{DMSO}-d_6$, δ): 1.19 (6H, d, $J=6.60$ Hz), 2.85 (3H, s), 5.13 (2H, 7-plet), 6.77 (1H, d, $J=9.53$ Hz), 7.09 (1H, d, $J=9.53$ Hz),

- 25 7.18-7.41 (4H, m), 7.63 (2H, br.s)

Elemental Analysis for $\text{C}_{18}\text{H}_{18}\text{FN}_5\text{O}_2\text{S}$

Calcd.: C, 58.21; H, 4.88; N, 18.86

Found : C, 58.45; H, 4.95; N, 18.65

- 30 6-[2-amino-4-[4-(methylsulfinyl)phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone
mp: 221-223°C (chloroform - acetone)

IR (KBr): 3390, 3302, 3203, 1658, 1583, 1539 cm^{-1}

ESI/MS: 438 $[\text{M}+\text{Na}]^+$, 416 $[\text{M}+\text{H}]^+$

^1H NMR (CDCl_3 , δ): 1.20 (6H, d, $J=6.62$ Hz), 2.51 (3H, s), 2.68 (3H, s), 5.23-5.38 (4H, m), 6.76 (1H, d, $J=9.52$ Hz), 6.93 (1H, d, $J=9.52$ Hz), 7.46-7.61 (4H, m)

6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone

mp: 241-243°C (ethanol suspension)

10 IR (KBr): 3438, 3330, 3224, 1653, 1630, 1583, 1537 cm^{-1}

ESI/MS: 885 $[2\text{M}+\text{Na}]^+$, 454 $[\text{M}+\text{Na}]^+$, 432 $[\text{M}+\text{H}]^+$

^1H NMR (CDCl_3 , δ): 1.16 (6H, d, $J=6.60$ Hz), 2.52 (3H, s), 3.01 (3H, s), 5.17-5.35 (3H, m), 6.80 (1H, d, $J=9.52$ Hz), 6.99 (1H, d, $J=9.52$ Hz), 7.52 (2H, d, $J=8.34$ Hz), 7.89 (2H, d, $J=8.34$ Hz)

15 Example 153

6-{2-Amino-4-methoxy-6-[4-(methylsulfinyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared from

6-[2-amino-4-[4-(methylsulfinyl)-phenyl]-6-(methylthio)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and sodium methoxide according to a similar manner to that of Example 139.

mp: 127-130°C (chloroform - hexane)

IR (KBr): 3319, 3190, 1660, 1587, 1545 cm^{-1}

25 ESI/MS: 821 $[2\text{M}+\text{Na}]^+$, 422 $[\text{M}+\text{Na}]^+$

^1H NMR (CDCl_3 , δ): 0.87 (6H, d, $J=6.62$ Hz), 2.66 (3H, s), 3.95 (3H, s), 5.10 (1H, 7-plet, $J=6.62$ Hz), 5.22 (2H, br.s), 6.87 (1H, d, $J=9.52$ Hz), 7.32 (1H, d, $J=9.52$ Hz), 7.40-7.46 (2H, m), 7.54-7.60 (2H, m)

30 Example 154

6-{2-Amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared

from

6-[2-amino-4-[4-(methylsulfonyl)-phenyl]-6-(methylthio)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and sodium
methoxide according to a similar manner to that of Example
5 139.

mp: 148-151°C (acetone)

IR (KBr): 1660, 1633, 1587, 1566, 1547 cm⁻¹

ESI/MS: 853[2M+Na]⁺, 438[M+Na]⁺, 416[M+H]⁺

¹H NMR (CDCl₃, δ): 0.84(6H, d, J=6.62 Hz), 2.98(3H, s), 3.98(3H,
10 s), 5.10(1H, 7-plet, J=6.62 Hz), 5.20(2H, br.s), 6.89(1H, d,
J=9.54 Hz), 7.35(1H, d, J=9.54 Hz), 7.47(2H, d), 7.88(2H, d)

¹H NMR (DMSO-d₆, δ): 0.69(6H, d, J=6.60 Hz), 3.15(3H, s), 3.90(3H,
s), 4.90(1H, 7-plet, J=6.60 Hz), 6.91(1H, d, J=9.54 Hz), 7.12(2H,
br.s), 7.45(2H, d, J=8.32 Hz), 7.57(1H, d, J=9.54 Hz), 7.87(2H,
15 d, J=8.32 Hz)

Example 155

6-{2-Amino-4-methoxy-6-[4-(methylsulfonyl)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared
from

20 6-{2-amino-4-(methylsulfinyl)-6-[4-(methylsulfonyl)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone and sodium
methoxide according to a similar manner to that of Example
80.

mp: 148-151°C (acetone)

25 IR (KBr): 1660, 1633, 1587, 1566, 1547 cm⁻¹

ESI/MS: 853[2M+Na]⁺, 438[M+Na]⁺, 416[M+H]⁺

¹H NMR (CDCl₃, δ): 0.84(6H, d, J=6.62 Hz), 2.98(3H, s), 3.98(3H,
s), 5.10(1H, 7-plet, J=6.62 Hz), 5.20(2H, br.s), 6.89(1H, d,
J=9.54 Hz), 7.35(1H, d, J=9.54 Hz), 7.47(2H, d), 7.88(2H, d)

30 ¹H NMR (DMSO-d₆, δ): 0.69(6H, d, J=6.60 Hz), 3.15(3H, s), 3.90(3H,
s), 4.90(1H, 7-plet, J=6.60 Hz), 6.91(1H, d, J=9.54 Hz), 7.12(2H,
br.s), 7.45(2H, d, J=8.32 Hz), 7.57(1H, d, J=9.54 Hz), 7.87(2H,

d, J=8.32 Hz)

Example 156

6-[2-Amino-4-(benzylamino)-6-(4-fluorophenyl)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared
5 from 6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
benzylamine according to a similar manner to that of Example
120.

mp: 191-192°C (ethanol)

10 IR (KBr): 3494, 3352, 3302, 1660, 1631, 1585, 1566, 1552 cm⁻¹

ESI/MS: 453[M+Na]⁺, 431[M+H]⁺

¹H NMR (CDCl₃, δ): 1.12(6H, d, J=6.62 Hz), 4.63(2H, d, J=5.02
Hz), 5.00(2H, br.s), 5.22(1H, 7-plet, J=6.62 Hz), 6.46(1H,
d, J=9.56 Hz), 6.99(1H, d, J=9.56 Hz), 6.97-7.44(10H, m)

15 Example 157

6-{2-Amino-4-(4-fluorophenyl)-6-[(2-pyridinylmethyl)
amino]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was
prepared from

6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-
20 5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and
2-pyridinylmethylaniline according to a similar manner to that
of Example 120.

mp: 210-212°C (ethanol)

IR (KBr): 3375, 3303, 1660, 1589, 1552 cm⁻¹

25 ESI/MS: 454[M+Na]⁺, 432[M+H]⁺

¹H NMR (CDCl₃, δ): 1.40(6H, d, J=6.63 Hz), 4.79(2H, d, J=4.64
Hz), 4.98(2H, br.s), 5.34(1H, 7-plet, J=6.63 Hz), 6.51(1H,
d, J=9.56 Hz), 6.57(1H, d, J=9.56 Hz), 6.96-7.06(2H, m),
7.21-7.43(4H, m), 7.63-7.69(2H, m), 8.50-8.53(1H, m)

30 Example 158

6-[2-Amino-4-anilino-6-(4-fluorophenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared from
6-[2-amino-4-(4-fluorophenyl)-6-(methylsulfinyl)-

5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone and aniline
(according to a similar manner to that of Example 133.

mp: >250°C (ethanol suspension)

IR (KBr): 3450, 3305, 3192, 1657, 1628, 1601, 1581, 1552 cm⁻¹

5 ESI/MS: 417[M+H]⁺

¹H NMR (CDCl₃, δ): 1.51(6H, d, J=6.63 Hz), 5.07(2H, br.s), 5.43(1H, 7-plet, J=6.63 Hz), 6.52(1H, d, J=9.62 Hz), 6.59(1H, d, J=9.62 Hz), 7.00-7.59(9H, m), 8.91(1H, s)

Example 159

10 A mixture of

6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-
2-isopropyl-3(2H)-pyridazinone (324 mg) and sodium hydride
(60 % in oil suspension) (42 mg) in N,N-dimethylacetamide (1
ml) was heated at 50-55°C for 30 minutes. tert-Butyl bromoacetate
15 (163 ml) was added to the mixture and the mixture was stirred
at the same temperature for 3 hours. Water (5 ml) was added,
stirred at ambient temperature and removed by decantation to
give syrup. The syrup was purified by column chromatography
on silica gel. With an elution of a mixture of n-hexane and
20 ethyl acetate (50 : 50 v/v) was given tert-butyl
{[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-
6-phenyl-4-pyrimidinyl]oxy}acetate as a solid (50 mg). With
an elution of ethyl acetate was given tert-butyl
[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-
25 6-oxo-4-phenyl-1(6H)-pyrimidinyl]acetate as a solid (265 mg).

tert-butyl {[2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-
3-pyridazinyl)-6-phenyl-4-pyrimidinyl]-oxy}acetate

mp: 160-162°C (acetone)

30 IR (KBr): 3431, 3309, 3195, 1745, 1658, 1635, 1591, 1545 cm⁻¹

ESI/MS: 460[M+Na]⁺, 438[M+H]⁺

¹H NMR (CDCl₃, δ): 0.88(6H, d, J=6.62 Hz), 1.50(9H, s), 4.80(2H, s), 5.10(1H, 7-plet, J=6.62 Hz), 5.12(2H, br.s), 6.87(1H, d,

J=9.52 Hz), 7.23-7.29(5H, m), 7.45(1H, d, J=9.52 Hz)

Elemental Analysis for C₂₃H₂₇N₅O

Calcd.: C, 63.14; H, 6.22; N, 16.01

Found : C, 63.09; H, 6.29; N, 15.90

5

tert-butyl [2-amino-5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-6-oxo-4-phenyl-1(6H)-pyrimidinyl]acetate
mp: 138-141°C (acetone suspension)

IR (KBr): 3342, 3219, 1755, 1705, 1645, 1583, 1535 cm⁻¹

10 ESI/MS: 897[2M+Na]⁺, 460[M+Na]⁺, 438[M+H]⁺

¹H NMR (CDCl₃, δ): 0.84(6H, d, J=6.60 Hz), 1.52(9H, s), 4.75(2H, s), 5.06(1H, 7-plet, J=6.60 Hz), 5.38(2H, br.s), 6.86(1H, d, J=9.52 Hz), 7.25-7.28(5H, m), 7.46(1H, d, J=9.52 Hz)

Example 160

15 6-[2-amino-4-(2-oxopropoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone and 1-chloroacetone according to a similar manner to that of Example 159.

20 ESI/MS: 781[2M+Na]⁺, 402[M+Na]⁺, 380[M+H]⁺

¹H NMR (CDCl₃, δ): 0.92(6H, d, J=6.62 Hz), 2.21(3H, s), 4.94(2H, s), 5.11(1H, 7-plet, J=6.62 Hz), 5.19(2H, br.s), 6.86(1H, d, J=9.50 Hz), 7.26-7.29(5H, m), 7.40(1H, d, J=9.50 Hz)

Example 161

25 6-[2-Amino-4-(2-oxo-2-phenylethoxy)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared from 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone and 2-bromo-1-phenylethanone according to a similar manner to that of Example 159.

30 mp: 182-183°C (diisopropyl ether - hexane)

IR (KBr): 3375, 3168, 1709, 1660, 1587 cm⁻¹

ESI/MS: 905[2M+Na]⁺, 464[M+Na]⁺, 442[M+H]⁺

¹H NMR (CDCl₃, δ): 0.90 (6H, d, J=6.60 Hz), 5.05 (2H, br. s), 5.10 (1H, 7-plet, J=6.60 Hz), 5.69 (2H, s), 6.87 (1H, d, J=9.52 Hz), 7.26-7.28 (5H, m), 7.48-7.70 (4H, m), 7.95-8.01 (2H, m)

Example 162

5 6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (62.4 mg) was dissolved in pyridine (5 ml). To the solution was added isoamyloyl chloride (32 mg) at 25°C. The solution was stirred for 2 hour at 25°C. The reaction mixture was added to a mixture of water and ethyl acetate. The organic
10 layer was separated and washes with brine, dried over magnesium sulfate. Evaporation of solvent gave an oily residue. The residue was dissolved in chloroform and submitted to silica gel (31.4 ml) column. The column was eluted with chloroform-methanol (9:1). Evaporation of solvent of the fractions containing
15 product gave crystals. Recrystallization from 80%-aqueous ethanol gave pure crystals of

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-3-methylbutanamide (33.4 mg)

¹H NMR (DMSO-d₆, δ): 0.94 (6H, d, J=6.6 Hz), 1.04 (6H, d, J=6.6
20 Hz), 2.03-2.16 (1H, m), 2.42 (2H, d, J=7 Hz), 5.05 (1H, m), 6.90 (1H, d, J=9.6 Hz), 7.34 (1H, d, J=9.6 Hz), 7.43 (5H, s), 8.85 (1H, s), 10.8 (1H, s)

ESI/MS: 392 [M+H]⁺, 414 [M+Na]⁺

IR (KBr): 3255, 2958, 1722, 1660, 1589, 1484, 1446 cm⁻¹

25 mp: 161°C (aq-EtOH)

Example 163

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-2-methylpropanamide was prepared according to a similar manner to that of Example 162.

30 ¹H NMR (DMSO-d₆, δ): 1.04 (6H, d, J=6.6 Hz), 1.10 (6H, d, J=6.8 Hz), 2.84-2.98 (1H, m), 5.05 (1H, m), 6.90 (1H, d, J=9.6 Hz), 7.34 (1H, d, J=9.6 Hz), 7.43 (5H, s), 8.85 (1H, s), 10.8 (1H, s)

ESI/MS: 378[M+H]⁺, 400[M+Na]⁺

IR (KBr): 3255, 2958, 1730, 1660, 1587, 1484, 1446 cm⁻¹

mp: 145-147°C (aq-EtOH)

Example 164

5 N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]butanamide was prepared according to a similar manner to that of Example 162.

¹H NMR (DMSO-d₆, δ): 0.92(3H, d, J=7.4 Hz), 1.04(6H, d, J=6.6 Hz), 1.56-1.67(2H, m), 2.53(2H, t, J=7.4 Hz), 5.05(1H, m),
10 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz), 7.43(5H, s), 8.85(1H, s), 10.8(1H, s)

ESI/MS: 378[M+H]⁺, 400[M+Na]⁺

IR (KBr): 3255, 2958, 1725, 1660, 1583, 1484, 1446 cm⁻¹

mp: 148-150°C (aq-EtOH)

15 Example 165

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]cyclohexanecarboxamide was prepared according to a similar manner to that of Example 162.

¹H NMR (DMSO-d₆, δ): 1.04(6H, d, J=6.6 Hz), 1.18-1.87(10H, m),
20 2.69-2.74(1H, m), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.31(1H, d, J=9.6 Hz), 7.43(5H, s), 8.84(1H, s), 10.7(1H, s)

ESI/MS: 418[M+H]⁺, 440[M+Na]⁺

IR (KBr): 3255, 2956, 1732, 1660, 1585, 1484, 1446 cm⁻¹

mp: 195-198°C (aq-EtOH)

25 Example 166

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-2-methoxyacetamide was prepared according to a similar manner to that of Example 162.

¹H NMR (DMSO-d₆, δ): 1.04(6H, d, J=6.6 Hz), 3.36(3H, s), 4.31(2H, s), 5.05(1H, m), 6.90(1H, d, J=9.6 Hz), 7.34(1H, d, J=9.6 Hz),
30 7.43(5H, s), 8.89(1H, s), 11.1(1H, s)

ESI/MS: 380[M+H]⁺, 402[M+Na]⁺

IR (KBr): 3250, 2955, 1730, 1660, 1580, 1484, 1446 cm^{-1}

mp: 94-97°C (aq-EtOH)

Example 167

5 N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]cyclopropanecarboxamide was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO- d_6 , δ): 0.85(4H, d, $J=5.6$ Hz), 1.04(6H, d, $J=6.6$ Hz), 2.19(1H, t, $J=5.6$ Hz), 5.05(1H, m), 6.90(1H, d, $J=9.6$ Hz), 7.34(1H, d, $J=9.6$ Hz), 7.43(5H, s), 8.89(1H, s), 11.1(1H, s)

ESI/MS: 398[M+Na] $^+$

IR (KBr): 3255, 2958, 1722, 1663, 1590, 1484, 1446 cm^{-1}

mp: 143-147°C (aq-EtOH)

Example 168

15 Methyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinylcarbamate was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO- d_6 , δ): 1.04(6H, d, $J=6.6$ Hz), 3.70(2H, s), 5.05(1H, m), 6.90(1H, d, $J=9.6$ Hz), 7.34(1H, d, $J=9.6$ Hz), 7.43(5H, s), 8.83(1H, s), 10.73(1H, s)

ESI/MS: 366[M+H] $^+$, 388[M+Na] $^+$

IR (KBr): 3255, 2958, 1722, 1660, 1589, 1484, 1446 cm^{-1}

mp: 197-200°C (aq-EtOH)

Example 169

25 N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO- d_6 , δ): 1.05(6H, d, $J=6.6$ Hz), 5.05(1H, m), 6.93(1H, d, $J=9.6$ Hz), 7.40(1H, d, $J=9.6$ Hz), 7.44(5H, s), 7.44-7.66(3H, m), 8.00(2H, m), 8.89(1H, s), 11.1(1H, s)

ESI/MS-Neg: 410[M-H] $^-$

IR (KBr): 3305, 2976, 1690, 1660, 1585, 1481, 1442 cm^{-1}

mp: 116-120°C (aq-EtOH)

Example 170

4-Fluoro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 162.

¹H NMR (DMSO-d₆, δ): 1.05(6H, d, J=6.6 Hz), 5.05(1H, m), 6.93(1H, d, J=9.6 Hz), 7.32-7.44(4H, m), 7.40(1H, d, J=9.6 Hz), 7.44(5H, s), 8.89(1H, s), 11.1(1H, s)

ESI/MS: 430[M+H]⁺, 452[M+Na]⁺

IR (KBr): 3305, 1660, 1585, 1481 cm⁻¹

mp: 106-110°C (aq-EtOH)

Example 171

4-Chloro-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 162.

¹H NMR (DMSO-d₆, δ): 1.05(6H, d, J=6.6 Hz), 5.06(1H, m), 6.92(1H, d, J=9.6 Hz), 7.39(1H, d, J=9.6 Hz), 7.44(5H, s), 7.60(2H, d, J=8.4 Hz), 8.01(2H, d, J=8.4 Hz), 8.95(1H, s), 11.4(1H, s)

ESI/MS: 446[M+H]⁺, 468[M+Na]⁺

IR (KBr): 3300, 1665, 1575, 1470 cm⁻¹

mp: 100°C (aq-EtOH)

Example 172

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methoxybenzamide was prepared according to a similar manner to that of Example 162.

¹H NMR (DMSO-d₆, δ): 1.05(6H, d, J=6.6 Hz), 3.85(3H, s), 5.06(1H, m), 6.91(1H, d, J=9.6 Hz), 7.05(2H, d, J=8.8 Hz), 7.39(1H, d, J=9.6 Hz), 8.02(2H, d, J=8.8 Hz), 7.49(5H, s), 8.93(1H, s), 11.1(1H, s)

ESI/MS: 442[M+H]⁺, 464.1[M+Na]⁺

IR (KBr): 3250, 1670, 1580, 1470 cm⁻¹

mp: 171-174°C (aq-EtOH)

Example 173

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-
4-phenyl-2-pyrimidinyl]-4-methylbenzamide was prepared
5 according to a similar manner to that of Example 162.

^1H NMR (DMSO- d_6 , δ): 1.05 (6H, d, $J=6.6$ Hz), 2.40 (3H, s), 5.06 (1H, m), 6.92 (1H, d, $J=9.6$ Hz), 7.33 (2H, d, $J=8.0$ Hz), 7.39 (1H, d, $J=9.6$ Hz), 7.49 (5H, s), 7.92 (2H, d, $J=8.0$ Hz), 8.93 (1H, s), 11.2 (1H, s)

10 ESI/MS: 426 $[\text{M}+\text{H}]^+$, 448 $[\text{M}+\text{Na}]^+$

IR (KBr): 3350, 1675, 1560, 1475 cm^{-1}

mp: 116°C (aq-EtOH)

Example 174

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-
15 4-phenyl-2-pyrimidinyl]-4-(trifluoromethyl)benzamide was prepared according to a similar manner to that of Example 162.

^1H NMR (DMSO- d_6 , δ): 1.05 (6H, d, $J=6.6$ Hz), 5.06 (1H, m), 6.93 (1H, d, $J=9.6$ Hz), 7.40 (1H, d, $J=9.6$ Hz), 7.42 (5H, s), 7.90 (2H, d, $J=8.4$ Hz), 8.15 (2H, d, $J=8.4$ Hz), 8.95 (1H, s), 11.5 (1H, s)
20

ESI/MS: 480 $[\text{M}+\text{H}]^+$, 502 $[\text{M}+\text{Na}]^+$

IR (KBr): 3320, 1685, 1555, 1484 cm^{-1}

mp: 160-163°C (aq-EtOH)

Example 175

25 6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (122.8 mg) was dissolved in pyridine (10 ml). To the solution was added 3-picoly l chloride hydrochloride (142 mg) at room temperature. The solution was stirred for 2 hours, and stood overnight.
30 Concentration of the above reaction mixture gave crystal residue. To the residue was added H_2O (20 ml). Crystals were precipitated and collected by filtration. Recrystallization from 5%-aqueous ethanol gave pure crystals of

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]nicotinamide (157 mg).

¹H NMR (DMSO-d₆, δ): 1.05 (6H, d, J=6.6 Hz), 5.05 (1H, m), 6.93 (1H, d, J=9.6 Hz), 7.39 (1H, d, J=9.6 Hz), 7.44 (5H, s), 7.53-7.60 (1H, m), 8.30-8.36 (1H, m), 8.77-8.80 (1H, m), 8.96 (1H, s), 9.11 (1H, d, J=2 Hz), 11.5 (1H, s)

ESI/MS: 413[M+H]⁺, 435[M+Na]⁺

IR (KBr): 3473, 2989, 1695, 1664, 1589, 1479, 1440 cm⁻¹

mp: 163-167°C (aq-EtOH)

10 Example 176

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (122.8 mg) was dissolved in dichloromethane (10 ml). To the solution were added pivaloyl chloride (96.5 mg) and diisopropyl ethyl amine (207 mg) at 25°C. The solution was stirred for 2 hours, and stood overnight. Concentration of the above reaction mixture gave oily residue. The residue was added to a mixture of water and ethyl acetate. The organic layer was separated, and washed with brine, dried over magnesium sulfate. Evaporation of solvent gave an oily residue. The residue was pulverized with diisoprppyl ether (10 ml) to give N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-2,2-dimethylpropanamide (142 mg).

¹H NMR (DMSO-d₆, δ): 1.04 (6H, d, J=6.6 Hz), 1.25 (9H, s), 5.05 (1H, m), 6.90 (1H, d, J=9.6 Hz), 7.36 (1H, d, J=9.6 Hz), 7.44 (5H, s), 8.88 (1H, s), 10.3 (1H, s)

ESI/MS: 392[M+H]⁺, 414[M+Na]⁺

IR (KBr): 3253, 2973, 1706, 1654, 1571, 1482, 1446 cm⁻¹

mp: 138-141°C (IPE)

Example 177

30 2,2,2-trichloroethyl

5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinylcarbamate was prepared according to a similar manner to that of Example 176.

^1H NMR (DMSO- d_6 , δ): 1.05 (6H, d, $J=6.6$ Hz), 4.94 (2H, s), 5.05 (1H, m), 6.90 (1H, d, $J=9.6$ Hz), 7.35 (1H, d, $J=9.6$ Hz), 7.44 (5H, s), 8.88 (1H, s), 11.2 (1H, s),

ESI/MS: 482 $[\text{M}+\text{H}]^+$, 504 $[\text{M}+\text{Na}]^+$

5 IR (KBr): 3253, 2973, 1745, 1654, 1571, 1482, 1446 cm^{-1}
mp: 158–162°C (IPE)

Example 178

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (61.4 mg) was dissolved in dichloromethane (10 ml). To the solution were added benzoyl chloride (56.2 mg) and diisopropyl ethyl amine (103 mg) at 25°C. The solution was stirred for 5 hours. Concentration of the above reaction mixture gave oily residue. The residue was added to a mixture of water and ethyl acetate. The organic layer was separated, and washed with brine, dried over magnesium sulfate. Evaporation of solvent gave an oily residue. The residue was purified with column chromatography on silica gel to give N-benzoyl-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide, which was crystallized from 90%-aqueous ethanol (59.5mg).

^1H NMR (DMSO- d_6 , δ): 1.04 (6H, d, $J=6.0$ Hz), 5.01 (1H, m), 7.04–7.05 (2H, m), 7.29–7.40 (4H, m), 7.49–7.70 (6H, m), 7.83–7.87 (4H, m), 8.99 (1H, s)

ESI/MS: 516 $[\text{M}+\text{H}]^+$, 538 $[\text{M}+\text{Na}]^+$

25 IR (KBr): 3255, 1655, 1570, 1475, 1440 cm^{-1}
mp: 121–125°C (aq-EtOH)

Example 179

4-Fluoro-N-(4-fluorobenzoyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO- d_6 , δ): 1.00 (6H, d, $J=6.6$ Hz), 5.02 (1H, m), 6.87 (1H,

d, $J=9.6$ Hz), 7.10-7.15 (2H, m), 7.32-7.42 (8H, m), 7.90-7.98 (4H, m), 9.00 (1H, s)

ESI/MS: 552 $[M+H]^+$, 574 $[M+Na]^+$

IR (KBr): 3255, 1665, 1565, 1470, 1445 cm^{-1}

5 mp: 148-151°C (aq-EtOH)

Example 180

4-Chloro-N-(4-chlorobenzoyl)-N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO- d_6 , δ): 1.00 (6H, d, $J=6.6$ Hz), 5.01 (1H, m), 6.81 (1H, d, $J=9.8$ Hz), 7.10-7.15 (2H, m), 7.32-7.42 (3H, m), 7.51 (4H, d, $J=8.6$ Hz), 7.87 (4H, d, $J=8.6$ Hz), 9.00 (1H, s)

ESI/MS: 584, 586 $[M+H]^+$, 606, 608 $[M+Na]^+$

15 IR (KBr): 3255, 1670, 1570, 1470, 1440 cm^{-1}

mp: 110°C (aq-EtOH)

Example 181

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methoxy-N-(4-methoxybenzoyl) benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO- d_6 , δ): 0.99 (6H, d, $J=6.6$ Hz), 3.82 (6H, s), 5.02 (1H, m), 6.91 (1H, d, $J=9.6$ Hz), 7.05 (4H, d, $J=9.0$ Hz), 7.12-7.16 (2H, m), 7.34-7.41 (4H, m), 7.80 (4H, d, $J=9.0$ Hz), 8.96 (1H, s),

25 ESI/MS: 576 $[M+H]^+$, 598 $[M+Na]^+$

IR (KBr): 3265, 1672, 1575, 1465, 1440 cm^{-1}

mp: 171-174°C (EtOH)

Example 182

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-methyl-N-(4-methylbenzoyl) benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO- d_6 , δ): 1.00 (6H, d, $J=6.6$ Hz), 2.30 (6H, s), 5.02 (1H, m), 6.91 (1H, d, $J=9.6$ Hz), 7.01-7.39 (10H, m), 7.72-7.88 (4H, m), 8.97 (1H, s)

ESI/MS: 544 $[\text{M}+\text{H}]^+$, 566 $[\text{M}+\text{Na}]^+$

5 IR (KBr): 3265, 1675, 1570, 1470, 1445 cm^{-1}

mp: 159°C (aq-EtOH)

Example 183

N-[5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinyl]-4-(trifluoromethyl)-

10 N-[4-(trifluoromethyl)benzoyl]benzamide was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO- d_6 , δ): 0.95 (6H, d, $J=6.6$ Hz), 5.00 (1H, m), 6.93 (1H, d, $J=9.6$ Hz), 7.01-7.05 (2H, m), 7.30-7.44 (4H, m), 8.09 (4H, d, $J=8.4$ Hz), 9.03 (1H, s),

15 ESI/MS: 652 $[\text{M}+\text{H}]^+$, 674 $[\text{M}+\text{Na}]^+$

IR (KBr): 3265, 1674, 1564, 1475, 1440 cm^{-1}

mp: 159°C (aq-EtOH)

Example 184

Dimethyl 5-(1-isopropyl-6-oxo-1,6-dihydro-3-pyridazinyl)-4-phenyl-2-pyrimidinylimidodicarbonate was prepared according to a similar manner to that of Example 178.

^1H NMR (DMSO- d_6 , δ): 1.01 (6H, d, $J=6.6$ Hz), 3.80 (6H, s), 5.04 (1H, m), 6.97 (1H, d, $J=9.6$ Hz), 7.48 (5H, s), 7.52 (1H, d, $J=9.6$ Hz), 9.12 (1H, s)

25 ESI/MS: 424 $[\text{M}+\text{H}]^+$, 446 $[\text{M}+\text{Na}]^+$

IR (KBr): 3265, 1694, 1550, 1460, 1440 cm^{-1}

mp: 216°C (aq-EtOH)

Example 185

To 1M-borontribromide solution in methylene chloride (70 ml) was added 6-[2-amino-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (4.72 g) at 5-10°C. The reaction mixture was stirred at room temperature for 2 hours. The mixture

was cooled in ice bath. To the cooled solution was added water. Organic layer was separated and concentrated in vacuo to give oily residue. To the residue was added the above separated aqueous layer. PH of the aqueous solution was adjusted to 6-7
5 with 10%-NaOH aqueous solution. White crystals were precipitated. The suspension was stirred at room temperature for 2 hours, at 0-5°C for 1 hour, and stood in the refrigerator overnight. The crystals were collected by filtration and dried in vacuo at 35-40°C, to give

10 6-[2-amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (4.45g).

¹H NMR (DMSO-d₆, δ): 1.17(6H, d, J=6.8 Hz), 5.06-5.12(1H, m),
6.74(2H, d, J=8.6 Hz), 6.77(1H, d, J=9.6 Hz), 6.95(2H, s),
7.03(1H, d, J=9.6 Hz), 7.20(2H, d, J=8.6 Hz), 8.35(1H, s),
15 9.80(1H, brs)

ESI/MS: 342[M+H]⁺, 346[M+Na]⁺

IR (KBr): 3149, 1652, 1583, 1479, 1407 cm⁻¹

mp: 246°C (H₂O)

Example 186

20 6-[2-Amino-4-(2-hydroxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 185.

¹H NMR (DMSO-d₆, δ): 1.11(6H, d, J=6.6 Hz), 5.03-5.10(1H, m),
6.70-6.80(4H, m), 6.99(2H, brs), 7.08-7.20(2H, m), 8.42(1H,
25 s), 9.53(1H, s)

ESI/MS: 342[M+H]⁺, 346[M+Na]⁺

IR (KBr): 3166, 1656, 1573, 1500, 1286 cm⁻¹

mp: 241°C (H₂O)

Example 187

30 6-[2-Amino-4-(3-hydroxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 185.

^1H NMR (DMSO- d_6 , δ): 0.98 (6H, d, $J=6.6$ Hz), 4.95-5.01 (1H, m), 6.72-6.89 (3H, m), 6.99 (2H, brs), 7.14-7.30 (3H, m), 8.40 (1H, s), 9.72 (1H, s)

ESI/MS: 342[M+H] $^+$, 346[M+Na] $^+$

5 IR (KBr): 3181, 1654, 1581, 1484 cm^{-1}

mp: 204°C (H_2O)

Example 188

6-[2-Amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (97 mg) was dissolved in
10 N,N-dimethylformamide (5 ml). To the solution were added ethyl
bromide (36 mg) and potassium tert-butoxide (36.9 mg) at 25°C.
The reaction mixture was stirred for 15 hours at ambient
temperature. The reaction mixture was added to a mixture of
water and ethyl acetate. The organic layer was separated and
15 washed with brine. The aqueous layer was combined and extracted
with ethyl acetate. The organic layer was combined and passed
through the diatomaceous earth column. Evaporation of solvent
at reduced pressure gave a residue. The residue was purified
with column chromatography on silica gel (methanol: chloroform
20 5:95 - 10:90) to give 6-[2-amino-4-(4-ethoxyphenyl)-
5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone, which was
crystallized from 90% aq-ethanol (27.5 mg)

^1H NMR (DMSO- d_6 , δ): 1.14 (6H, d, $J=6.6$ Hz), 1.31 (3H, t, $J=7.0$
Hz), 4.02 (2H, q, $J=7.0$ Hz), 5.01-5.14 (1H, m), 6.73 (1H, d, $J=9.6$
25 Hz), 6.92 (2H, d, $J=8.8$ Hz), 7.05 (2H, s), 7.25 (1H, d, $J=9.6$
Hz), 8.38 (1H, s)

ESI/MS: 352[M+H] $^+$, 374[M+Na] $^+$

IR (KBr): 3374, 1645, 1585, 1405 cm^{-1}

mp: 204°C (aq-EtOH)

30 Example 189

6-[2-Amino-4-(2-ethoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

^1H NMR (DMSO- d_6 , δ): 0.93(6H, brs), 1.00(3H, t), 3.7(2H, brs), 4.92-4.99(1H, m), 6.80(1H, d, $J=9.6$ Hz), 6.97(2H, brs), 6.88-7.08(2H, m), 7.25(1H, d, $J=9.6$ Hz), 7.29-7.43(2H, m), 8.43(1H, s)

5 ESI/MS: 352[M+H] $^+$, 374[M+Na] $^+$

IR (KBr): 3193, 1641, 1575, 1482 cm^{-1}

mp: 185°C (aq-EtOH)

Example 190

6-[2-Amino-4-(3-ethoxyphenyl)-5-pyrimidinyl]-

10 2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO- d_6 , δ): 1.08(6H, d, $J=6.6$ Hz), 1.26(3H, t, $J=7.0$ Hz), 3.93(2H, q, $J=7.0$ Hz), 5.02-5.08(1H, m), 6.80(1H, d, $J=9.6$ Hz), 6.85-6.96(3H, m), 7.06(2H, s), 7.14(1H, d, $J=9.6$ Hz),
15 7.27(1H, t, $J=8.0$ Hz), 8.44(1H, s)

ESI/MS: 352[M+H] $^+$, 374[M+Na] $^+$

IR (KBr): 3307, 1620, 1585, 1482 cm^{-1}

mp: 142°C (aq-EtOH)

Example 191

20 6-[2-Amino-4-(4-propoxyphenyl)-5-pyrimidinyl]-

2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO- d_6 , δ): 0.96(3H, t, $J=7.4$ Hz), 1.14(6H, d, $J=6.6$ Hz), 1.66-1.77(2H, m), 3.93(2H, d, $J=6.6$ Hz), 5.02-5.12(1H, m),
25 6.79(1H, d, $J=9.6$ Hz), 6.93(2H, d, $J=8.8$ Hz), 7.00(2H, s), 7.08(1H, d, $J=9.6$ Hz), 7.30(2H, d, $J=8.8$ Hz), 8.34(1H, s)

ESI/MS: 366[M+H] $^+$

IR (KBr): 3376, 1641, 1585, 1482 cm^{-1}

30 mp: 175°C (aq-EtOH)

Example 192

6-[2-Amino-4-(2-propoxyphenyl)-5-pyrimidinyl]-

2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.72 (3H, t), 0.95-1.04 (6H, m), 1.34-1.43 (2H, m), 3.57-3.61 (2H, m), 4.92-4.99 (1H, m), 6.78 (1H, d, J=9.6 Hz), 6.92 (1H, d, J=8.4 Hz), 6.98 (2H, s), 7.03 (2H, m, J=t Hz), 7.22 (1H, d, J=9.6 Hz), 7.31-7.40 (2H, m), 8.46 (1H, s)

ESI/MS: 366[M+H]⁺

IR (KBr): 3421, 1648, 1573, 1452 cm⁻¹

mp: 145°C (aq-EtOH)

10 Example 193

6-[2-Amino-4-(3-propoxyphenyl)-5-pyrimidinyl]-

2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.92 (3H, t, J=7.4 Hz), 1.08 (6H, d, J=6.6 Hz), 1.60-1.67 (2H, m), 3.83 (2H, t, J=7.4 Hz), 5.05 (1H, m), 6.80 (1H, d, J=9.6 Hz), 6.84-6.91 (3H, m), 7.07 (2H, s), 7.14 (1H, d, J=9.6 Hz), 7.24 (1H, t, J=7.6 Hz), 8.44 (1H, s)

ESI/MS: 366[M+H]⁺, 388[M+Na]⁺

IR (KBr): 3194, 1660, 1575, 1484 cm⁻¹

20 mp: 122°C (aq-EtOH)

Example 194

6-[2-Amino-4-(4-isopropoxyphenyl)-5-pyrimidinyl]-

2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 1.12 (6H, d, J=6.6 Hz), 1.25 (6H, d, J=6.0 Hz), 4.57-4.69 (1H, m), 5.01-5.14 (1H, m), 6.80 (1H, d, J=9.6 Hz), 6.91 (2H, d, J=8.8 Hz), 7.00 (2H, s), 7.12 (1H, d, J=9.6 Hz), 7.28 (2H, d, J=8.8 Hz), 8.38 (1H, s)

APCI/MS: 366[M+H]⁺

30 IR (KBr): 3180, 1643, 1569, 1481 cm⁻¹

mp: 164°C (aq-EtOH)

Example 195

6-[2-Amino-4-(2-isopropoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.72 (3H, t), 0.95-1.04 (6H, m), 1.34-1.43 (2H,
5 m), 3.57-3.61 (2H, m), 4.92-4.99 (1H, m), 6.78 (1H, d, J=9.6 Hz),
6.92 (1H, d, J=8.4 Hz), 6.98 (2H, s), 7.03 (2H, m, J=t Hz), 7.22 (1H,
d, J=9.6 Hz), 7.31-7.40 (2H, m), 8.46 (1H, s)

APCI/MS: 366[M+H]⁺

IR (KBr): 3421, 1648, 1573, 1452 cm⁻¹

10 mp: 202°C (aq-EtOH)

Example 196

6-[2-Amino-4-(3-isopropoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

15 ¹H NMR (DMSO-d₆, δ): 1.03 (6H, t, J=7.4 Hz), 1.17 (6H, d, J=6.6
Hz), 4.44-4.50 (1H, m), 5.01-5.08 (1H, m), 6.80 (1H, d, J=9.6
Hz), 6.81-6.94 (3H, m), 7.06 (2H, s), 7.16 (1H, d, J=9.6 Hz),
7.24-7.31 (2H, m), 8.44 (1H, s)

APCI/MS: 366[M+H]⁺

20 IR (KBr): 3191, 1648, 1573, 1492 cm⁻¹

mp: 143°C (aq-EtOH)

Example 197

6-[2-Amino-4-(4-butoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
25 similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.92 (3H, t, J=7.2 Hz), 1.14 (6H, d, J=6.6
Hz), 1.36-1.47 (2H, m), 1.61-1.71 (2H, m), 3.97 (2H, t, J=6.4
Hz), 5.04-5.11 (1H, m), 6.77 (1H, d, J=9.6 Hz), 6.93 (2H, d, J=8.8
Hz), 7.00 (2H, s), 7.03 (1H, d, J=9.6 Hz), 7.29 (2H, d, J=8.8
30 Hz), 8.38 (1H, s)

APCI/MS: 380[M+H]⁺

IR (KBr): 3384, 1641, 1583, 1484 cm⁻¹

mp: 143°C (aq-EtOH)

Example 198

6-[2-Amino-4-(2-butoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
5 similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.77(3H, t, J=7.6 Hz), 0.94-1.04(6H, m),
1.11-1.19(2H, m), 1.32-1.38(2H, m), 3.66(2H, m), 4.92-4.99(1H,
m), 6.79(1H, d, J=9.6 Hz), 6.92(2H, d, J=8.4 Hz), 6.98(2H,
s), 7.04(1H, t, J=7.2 Hz), 7.22(1H, d, J=9.6 Hz), 7.31-7.40(2H,
10 m), 8.45(1H, s)

APCI/MS: 380[M+H]⁺

IR (KBr): 3394, 1664, 1581, 1484 cm⁻¹

mp: 149°C (aq-EtOH)

Example 199

15 6-[2-Amino-4-(3-butoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.89(3H, t, J=7.2 Hz), 1.04(6H, t, J=6.6
Hz), 1.28-1.46(2H, m), 1.56-1.69(2H, m), 3.86(2H, t, J=6.4
20 Hz), 4.99-5.11(1H, m), 6.80(1H, d, J=9.6 Hz), 6.84-6.99(3H,
m), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.28(1H, t, J=8 Hz),
8.43(1H, s)

APCI/MS: 380[M+H]⁺

IR (KBr): 3313, 1646, 1577, 1471 cm⁻¹

25 mp: 130°C (aq-EtOH)

Example 200

6-[2-Amino-4-(4-isobutoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

30 ¹H NMR (DMSO-d₆, δ): 0.96(6H, d, J=6.6 Hz), 1.14(6H, d, J=6.6
Hz), 1.96(1H, m), 3.75(2H, t, J=6.4 Hz), 5.04-5.11(1H, m),
6.78(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, sd),

7.07 (1H, d, J=9.6 Hz), 7.30 (2H, d, J=8.8 Hz), 8.38 (1H, s)

APCI/MS: 380 [M+H]⁺

IR (KBr): 3386, 1639, 1585, 1484 cm⁻¹

mp: 166°C (aq-EtOH)

5 Example 201

6-[2-Amino-4-(2-isobutoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.72 (6H, d, J=6.8 Hz), 0.98-1.04 (6H, m),
10 1.62-1.68 (1H, m), 3.46 (2H, d, J=6.8 Hz), 4.93-4.99 (1H, m),
6.77 (1H, d, J=9.6 Hz), 6.93 (1H, d, J=8.0 Hz), 6.98 (2H, s),
7.03 (1H, t, J=7.2 Hz), 7.20 (1H, d, J=9.6 Hz), 7.31-7.40 (2H,
m), 8.49 (1H, s)

APCI/MS: 380 [M+H]⁺

15 IR (KBr): 3322, 1650, 1590, 1492 cm⁻¹

mp: 189°C (aq-EtOH)

Example 202

6-[2-Amino-4-(3-isobutoxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
20 similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.91 (6H, d, J=6.6 Hz), 1.08 (6H, d, J=6.6
Hz), 1.86-1.99 (2H, m), 3.63 (2H, d, J=6.6 Hz), 5.02-5.09 (1H,
m), 6.80 (1H, d, J=9.6 Hz), 6.84-6.97 (3H, m), 7.07 (2H, s), 7.13 (1H,
d, J=9.6 Hz), 7.28 (1H, t, J=7.8 Hz), 8.44 (1H, s)

25 APCI/MS: 380 [M+H]⁺

IR (KBr): 3315, 1666, 1573, 1486 cm⁻¹

mp: 137°C (aq-EtOH)

Example 203

6-{2-Amino-4-[4-(isopentyloxy)phenyl]-5-pyrimidinyl}-
30 2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.92 (6H, d, J=6.4 Hz), 1.13 (6H, d, J=6.6

Hz), 1.55-1.64 (2H, m), 1.7-1.80 (1H, m), 3.99 (2H, t, J=6.4 Hz), 5.05-5.11 (1H, m), 6.79 (1H, d, J=9.6 Hz), 6.93 (2H, d, J=8.8 Hz), 7.00 (2H, s), 7.08 (1H, d, J=9.6 Hz), 7.29 (2H, d, J=8.8 Hz), 8.38 (1H, s)

5 ESI/MS: 394[M+H]⁺, 416[M+Na]⁺

IR (KBr): 3383, 1640, 1586, 1480 cm⁻¹

mp: 164°C (aq-EtOH)

Example 204

10 6-{2-Amino-4-[2-(isopentyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.76 (6H, d, J=6.6 Hz), 0.96-1.05 (6H, m), 1.21-1.31 (2H, m), 1.40-1.50 (1H, m), 3.67 (2H, m), 4.92-4.99 (1H, m), 6.79 (1H, d, J=9.6 Hz), 6.92-7.08 (2H, m), 6.96 (2H, s), 7.24 (1H, d, J=9.6 Hz), 7.29-7.41 (2H, m), 8.46 (1H, s)

15 ESI/MS: 394[M+H]⁺, 416[M+Na]⁺

IR (KBr): 3325, 1655, 1585, 1488 cm⁻¹

mp: 155°C (aq-EtOH)

Example 205

20 6-{2-Amino-4-[3-(isopentyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.89 (6H, d, J=6.4 Hz), 1.08 (6H, d, J=6.6 Hz), 1.49-1.59 (2H, m), 1.65-1.75 (1H, m), 3.88 (2H, d, J=6.4 Hz), 5.01-5.08 (1H, m), 6.79 (1H, d, J=9.6 Hz), 6.83-6.96 (3H, m), 7.09 (2H, s), 7.14 (1H, d, J=9.6 Hz), 7.28 (1H, t, J=8.0 Hz), 8.44 (1H, s)

25 ESI/MS: 394[M+H]⁺, 416[M+Na]⁺

IR (KBr): 3310, 1656, 1570, 1480 cm⁻¹

30 mp: 97°C (aq-EtOH)

Example 206

6-{2-Amino-4-[4-(hexyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a

similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.87(3H, d, J=7.6 Hz), 1.14(6H, d, J=6.6 Hz), 1.25-1.63(6H, m), 3.96(2H, t, J=6.4 Hz), 5.01-5.15(1H, m), 6.78(1H, d, J=9.6 Hz), 6.93(2H, d, J=8.8 Hz), 7.00(2H, s), 7.08(1H, d, J=9.6 Hz), 7.29(2H, d, J=8.8 Hz), 8.38(1H, s)

ESI/MS: 408[M+H]⁺, 430[M+Na]⁺

IR (KBr): 3370, 1660, 1570, 1485 cm⁻¹

mp: 184°C (aq-EtOH)

10 Example 207

6-{2-Amino-4-[2-(hexyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 0.8(3H, d, J=6.8 Hz), 0.95(6H, m), 1.14-1.39(8H, m), 3.65(2H, m), 4.92-4.98(1H, m), 6.78(1H, d, J=9.6 Hz), 6.90-7.07(4H, m), 6.96(2H, s), 7.23(1H, d, J=9.6 Hz), 7.29-7.41(2H, m), 8.45(1H, s)

ESI/MS: 408[M+H]⁺, 430[M+Na]⁺

IR (KBr): 3325, 1655, 1585, 1488 cm⁻¹

20 mp: 92°C (aq-EtOH)

Example 208

6-{2-Amino-4-[3-(hexyloxy)phenyl]-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

25 ¹H NMR (DMSO-d₆, δ): 0.87(3H, t, J=6.8 Hz), 1.04(6H, d, J=8.4 Hz), 1.29-1.38(6H, m), 1.57-1.67(2H, m), 3.85(2H, t, J=6.4 Hz), 4.98-5.12(1H, m), 6.79(1H, d, J=9.6 Hz), 6.84-6.96(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.24-7.32(1H, m), 8.44(1H, s)

30 ESI/MS: 408[M+H]⁺, 430[M+Na]⁺

IR (KBr): 3330, 1660, 1580, 1485 cm⁻¹

mp: 121°C (aq-EtOH)

Example 209

6-{2-Amino-4-[4-(2-fluoroethoxy)phenyl]-5-pyrimidinyl}-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

- 5 ^1H NMR (DMSO- d_6 , δ): 1.14(6H, d, $J=6.6$ Hz), 4.15-4.17(2H, m),
4.30-4.34(2H, m), 5.05-5.11(1H, m), 6.79(1H, d, $J=9.6$ Hz),
6.98(2H, d, $J=8.8$ Hz), 7.06(2H, s), 7.08(1H, d, $J=9.6$ Hz),
7.32(2H, d, $J=8.8$ Hz), 8.39(1H, s)
ESI/MS: 370[M+H] $^+$, 392[M+Na] $^+$
10 IR (KBr): 3178, 1635, 1585, 1482 cm^{-1}
mp: 200°C (aq-EtOH)

Example 210

6-{2-Amino-4-[2-(2-fluoroethoxy)phenyl]-5-pyrimidinyl}-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
15 similar manner to that of Example 188.

- ^1H NMR (DMSO- d_6 , δ): 0.93-1.05(6H, m), 3.60-4.00(2H, m),
4.30-4.57(2H, m), 4.91-4.97(1H, m), 6.78(1H, d, $J=9.6$ Hz),
6.93-7.43(4H, m), 7.05(2H, s), 7.22(1H, d, $J=9.6$ Hz), 8.45(1H,
s)
20 ESI/MS: 370[M+H] $^+$, 392[M+Na] $^+$
IR (KBr): 3189, 1658, 1585, 1479 cm^{-1}
mp: 171°C (aq-EtOH)

Example 211

6-{2-Amino-4-[3-(2-fluoroethoxy)phenyl]-5-pyrimidinyl}-
25 2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 188.

- ^1H NMR (DMSO- d_6 , δ): 1.07(6H, d, $J=6.6$ Hz), 4.07-4.10(1H, m),
4.22-4.26(1H, m), 4.56-4.60(1H, m), 4.80-4.84(1H, m),
5.02-5.08(1H, m), 6.80(1H, d, $J=9.6$ Hz), 6.86-7.33(4H, m),
30 7.08(2H, s), 7.17(1H, d, $J=9.6$ Hz), 8.45(1H, s)
ESI/MS: 370[M+H] $^+$, 392[M+Na] $^+$
IR (KBr): 3183, 1641, 1575, 1487 cm^{-1}

mp: 123°C (aq-EtOH)

Example 212

6-{2-Amino-4-[4-(2-methoxyethoxy)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared
5 according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 1.14 (6H, d, J=6.6 Hz), 3.30 (3H, s), 3.62 (2H, m), 4.10 (2H, m), 5.05-5.11 (1H, m), 6.78 (1H, d, J=9.6 Hz), 6.95 (2H, d, J=8.8 Hz), 7.01 (2H, s), 7.07 (1H, d, J=9.6 Hz), 7.30 (2H, d, J=8.8 Hz), 8.39 (1H, s)

10 ESI/MS: 382[M+H]⁺, 404[M+Na]⁺

IR (KBr): 3328, 1666, 1563, 1475 cm⁻¹

mp: 147°C (aq-EtOH)

Example 213

6-{2-Amino-4-[3-(2-methoxyethoxy)phenyl]-
15 5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared
according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 1.01-1.09 (6H, m), 3.28 (3H, s), 3.57-3.61 (2H, m), 3.98-4.02 (2H, m), 5.01-5.08 (1H, m), 6.80 (1H, d, J=9.6 Hz), 6.86-6.99 (3H, m), 7.08 (2H, s), 7.15 (1H, d, J=9.6 Hz),
20 7.24-7.32 (1H, m), 8.44 (1H, s)

ESI/MS: 382[M+H]⁺, 404[M+Na]⁺

IR (KBr): 2960, 1671, 1573, 1471 cm⁻¹

Example 214

6-{2-Amino-4-[4-(3-fluoropropoxy)phenyl]-
25 5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared
according to a similar manner to that of Example 188.

¹H NMR (DMSO-d₆, δ): 1.14 (6H, d, J=6.6 Hz), 2.00-2.19 (2H, m), 4.08 (2H, t, J=6.2 Hz), 4.48 (1H, t, J=6.0 Hz), 4.71 (1H, t, J=6.2 Hz), 5.01-5.15 (1H, m), 6.78 (1H, d, J=9.6 Hz), 6.96 (2H, d, J=8.8 Hz), 7.01 (2H, s), 7.08 (1H, d, J=9.6 Hz), 7.31 (2H, d, J=8.8 Hz), 8.39 (1H, s)

30 ESI/MS: 384[M+H]⁺, 406[M+Na]⁺

IR (KBr): 3187, 1656, 1587, 1469 cm^{-1}

mp: 179°C (aq-EtOH)

Example 215

5 6-{2-Amino-4-[2-(3-fluoropropoxy)phenyl]-
5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO- d_6 , δ): 0.94(6H, brs), 1.61-1.88(2H, m), 3.78(2H, m), 4.21(1H, t, $J=6.0$ Hz), 4.44(1H, t, $J=6.0$ Hz), 4.92-4.99(1H, m), 6.78(1H, d, $J=9.6$ Hz), 6.89(2H, s), 6.94-7.09(2H, m), 7.24(1H, d, $J=9.6$ Hz), 7.31-7.41(2H, m), 8.46(1H, s)

ESI/MS: 384[M+H] $^+$, 406[M+Na] $^+$

IR (KBr): 3156, 1635, 1579, 1486 cm^{-1}

mp: 200°C (aq-EtOH)

Example 216

15 6-{2-Amino-4-[3-(3-fluoropropoxy)phenyl]-
-5-pyrimidinyl}-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 188.

^1H NMR (DMSO- d_6 , δ): 1.07(6H, d, $J=6.6$ Hz), 1.95-2.14(2H, m), 4.00(2H, t, $J=6.0$ Hz), 4.44(1H, t, $J=6.0$ Hz), 4.68(1H, t, $J=6.0$ Hz), 5.01-5.08(1H, m), 6.80(1H, d, $J=9.6$ Hz), 6.86-6.99(3H, m), 7.07(2H, s), 7.15(1H, d, $J=9.6$ Hz), 7.29(1H, t, $J=5.8$ Hz), 8.44(1H, s)

ESI/MS: 384[M+H] $^+$, 406[M+Na] $^+$

IR (KBr): 3191, 1658, 1575, 1485 cm^{-1}

25 mp: 123°C (aq-EtOH)

Example 217

30 6-[2-Amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone (97 mg) was dissolved in N,N-dimethylformamide (5 ml). To the solution were added 2-dimethylaminoethyl chloride hydrochloride (47.5 mg) and potassium tert-butoxide (73.9 mg) at 25°C. The reaction mixture was stirred for 15 hours at ambient temperature. The reaction mixture was added to a mixture of water and ethyl acetate.

The organic layer was separated and washed with brine. The aqueous layer was combined and extracted with ethyl acetate. The organic layer was combined and passed through the diatomaceous earth column. Evaporation of solvent under reduced pressure gave a residue. The residue was purified with column chromatography on silica gel (methanol:chloroform 10:90 - 20:80) to give

6-(2-amino-4-{4-[2-(dimethylamino)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone, which was crystallized from 90% aq-ethanol (36.3 mg).

^1H NMR (DMSO- d_6 , δ): 1.13 (6H, d, $J=6.6$ Hz), 2.20 (6H, s), 2.60 (2H, t, $J=6.0$ Hz), 4.05 (2H, t, $J=6.0$ Hz), 5.05-5.11 (1H, m), 6.78 (1H, d, $J=9.6$ Hz), 6.94 (2H, d, $J=8.8$ Hz), 7.00 (2H, s), 7.08 (1H, d, $J=9.6$ Hz), 7.30 (2H, d, $J=8.8$ Hz), 8.38 (1H, s).

ESI/MS: 395 $[\text{M}+\text{H}]^+$, 417 $[\text{M}+\text{Na}]^+$

IR (KBr): 3421, 1652, 1587, 1484 cm^{-1}

mp: 162°C (aq-EtOH)

Example 218

6-(2-Amino-4-{2-[2-(dimethylamino)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^1H NMR (DMSO- d_6 , δ): 0.95 (6H, brs), 2.23 (6H, s), 2.28 (2H, t, $J=5.6$ Hz), 3.73 (2H, brs), 5.05-5.11 (1H, m), 6.80 (1H, d, $J=9.6$ Hz), 6.96-7.08 (2H, m), 7.00 (2H, s), 7.27 (1H, d, $J=9.6$ Hz), 7.33-7.41 (2H, d), 8.45 (1H, s)

ESI/MS: 395 $[\text{M}+\text{H}]^+$, 417 $[\text{M}+\text{Na}]^+$

IR (KBr): 3160, 1664, 1573, 1457 cm^{-1}

mp: 198°C (aq-EtOH)

Example 219

6-(2-Amino-4-{3-[2-(dimethylamino)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^1H NMR (DMSO- d_6 , δ): 1.08 (6H, d, $J=6.6$ Hz), 2.16 (6H, s), 2.55 (2H, t, $J=5.6$ Hz), 3.94 (2H, t, $J=5.6$ Hz), 5.01-5.08 (1H, m), 6.80 (1H, d, $J=9.6$ Hz), 6.85-6.98 (3H, m), 7.07 (2H, s), 7.14 (1H, d, $J=9.6$ Hz), 7.24-7.32 (1H, d), 8.44 (1H, s)

5 ESI/MS: 395 $[\text{M}+\text{H}]^+$, 417 $[\text{M}+\text{Na}]^+$

IR (KBr): 3421, 1635, 1592, 1484 cm^{-1}

mp: 111°C (aq-EtOH)

Example 220

10 6-(2-Amino-4-{4-[2-(4-morpholinyl)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

^1H NMR (DMSO- d_6 , δ): 1.14 (6H, d, $J=6.6$ Hz), 2.45 (4H, t, $J=4.8$ Hz), 2.67 (2H, t, $J=5.6$ Hz), 3.56 (4H, t, $J=4.8$ Hz), 4.09 (2H, t, $J=5.6$ Hz), 5.05-5.11 (1H, m), 6.79 (1H, d, $J=9.6$ Hz), 6.95 (2H, d, $J=8.8$ Hz), 7.00 (2H, s), 7.08 (1H, d, $J=9.6$ Hz), 7.30 (2H, d, $J=8.8$ Hz), 8.38 (1H, s)

15 ESI/MS: 437 $[\text{M}+\text{H}]^+$, 459 $[\text{M}+\text{Na}]^+$

IR (KBr): 3309, 1662, 1589, 1479 cm^{-1}

mp: 161°C (aq-EtOH)

20 Example 221

6-(2-Amino-4-{2-[2-(4-morpholinyl)ethoxy]phenyl}-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

25 ^1H NMR (DMSO- d_6 , δ): 1.02 (6H, brs), 2.26 (4H, t, $J=4.4$ Hz), 2.36 (2H, t, $J=6.0$ Hz), 3.45 (4H, t, $J=4.4$ Hz), 3.75 (2H,), 5.05-5.11 (1H, m), 6.80 (1H, d, $J=9.6$ Hz), 6.93-7.08 (2H, m), 6.98 (2H, s), 7.29 (1H, d, $J=9.6$ Hz), 7.29-7.39 (2H, m), 8.45 (1H, s)

ESI/MS: 437 $[\text{M}+\text{H}]^+$, 459 $[\text{M}+\text{Na}]^+$

IR (KBr): 3334, 1648, 1575, 1479 cm^{-1}

30 mp: 115°C (aq-EtOH)

Example 222

6-(2-Amino-4-{3-[2-(4-morpholinyl)ethoxy]phenyl}-

5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 217.

¹H NMR (DMSO-d₆, δ): 1.02-1.10(6H, m), 2.42(4H, t, J=4.6 Hz), 2.62(2H, t, J=5.8 Hz), 3.55(4H, t, J=4.6 Hz), 3.98(2H, t, J=5.8 Hz), 5.05-5.11(1H, m), 6.80(1H, d, J=9.6 Hz), 6.85-6.98(3H, m), 7.07(2H, s), 7.14(1H, d, J=9.6 Hz), 7.24-7.32(1H, m), 8.43(1H, s)

ESI/MS: 437[M+H]⁺, 459[M+Na]⁺

IR (KBr): 3309, 1650, 1573, 1475 cm⁻¹

10 mp: 68°C (aq-EtOH)

Example 223

6-[2-Amino-4-(4-hydroxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 185.

15 ¹H NMR (DMSO-d₆, δ): 3.68(3H, s), 6.65-6.88(4H, m), 6.97(2H, brs), 7.26(2H, d, J=8.6 Hz), 8.33(1H, s), 9.87(1H, brs)

ESI/MS: 296[M+H]⁺, 318[M+Na]⁺

IR (KBr): 3180, 1641, 1573, 1481, 1411 cm⁻¹

mp: 250°C (H₂O)

20 Example 224

6-[2-Amino-4-(2-hydroxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 185.

¹H NMR (DMSO-d₆, δ): 3.58(3H, s), 6.71(1H, d, J=9.6 Hz), 6.76-6.88(2H, m), 6.95(1H, d, J=9.6 Hz), 7.05(2H, brs), 7.21-7.28(2H, m), 8.41(1H, s), 10.0(1H, s)

ESI/MS: 296[M+H]⁺, 318[M+Na]⁺

IR (KBr): 3180, 1646, 1579, 1496, 1440 cm⁻¹

mp: 260°C (H₂O)

30 Example 225

6-[2-Amino-4-(3-hydroxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner

to that of Example 185.

^1H NMR (DMSO- d_6 , δ): 3.68(3H, s), 6.69-6.83(5H, m), 7.06(2H, brs), 7.18(1H, t, $J=7.8$ Hz), 8.39(1H, s), 9.59(1H, s)

ESI/MS: 296[M+H] $^+$, 318[M+Na] $^+$

5 mp: 285°C (H₂O)

Example 226

6-[2-Amino-4-(4-bromophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

10 ^1H NMR (DMSO- d_6 , δ): 6.74(1H, d, $J=9.8$ Hz), 6.98(1H, d, $J=9.8$ Hz), 7.19(2H, s), 7.34(2H, d, $J=8.4$ Hz), 7.61(2H, d, $J=8.4$ Hz), 8.40(1H, s), 13.1(1H, s)

ESI/MS: 342, 344[M+H] $^+$

IR (KBr): 3316, 1683, 1583, 1473 cm^{-1}

15 Example 227

6-[2-Amino-4-(3-bromophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 6.75(1H, d, $J=10.0$ Hz), 7.03(1H, d, $J=9.6$ Hz), 7.15(2H, s), 7.27-7.38(2H, m), 7.61-7.66(2H, m), 8.42(1H, s)

ESI/MS: 366, 368[M+Na] $^+$

IR (KBr): 3320, 1625, 1583, 1471 cm^{-1}

Example 228

25 6-[2-Amino-4-(2,6-difluorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 6.80(1H, d, $J=9.6$ Hz), 7.10-7.24(3H, m), 7.21(1H, s), 7.30(1H, d, $J=9.6$ Hz), 7.48-7.55(1H, m), 8.55(1H, s), 12.95(1H, s)

30 ESI/MS: 324[M+Na] $^+$

Example 229

6-[2-Amino-4-(3,5-difluorophenyl)-5-pyrimidinyl]-
3(2H)-pyridazinone was prepared according to a similar manner
to that of Example 27.

¹H NMR (DMSO-d₆, δ): 6.78(1H, d, J=9.8 Hz), 7.03-7.11(3H, m),
5 7.18(2H, s), 7.30-7.41(1H, m), 8.45(1H, s), 13.1(1H, s)
ESI/MS: 302[M+H]⁺, 324[M+Na]⁺
IR (KBr): 3342, 1623, 1585, 1490 cm⁻¹

Example 230

6-[2-Amino-4-(2,6-dichlorophenyl)-5-pyrimidinyl]-
10 3(2H)-pyridazinone was prepared according to a similar manner
to that of Example 27.

¹H NMR (DMSO-d₆, δ): 6.78(1H, d, J=9.8 Hz), 7.19-7.24(3H, m),
7.40-7.55(3H, m), 8.58(1H, s), 12.96(1H, s)
ESI/MS: 356, 358[M+Na]⁺
15 IR (KBr): 3305, 1654, 1583, 1484 cm⁻¹

Example 231

6-[2-Amino-4-(2,6-dimethylphenyl)-5-pyrimidinyl]-
3(2H)-pyridazinone was prepared according to a similar manner
to that of Example 27.

20 ¹H NMR (DMSO-d₆, δ): 1.96(6H, s), 6.59(1H, d, J=9.8 Hz), 6.72(1H,
d, J=9.8 Hz), 7.04-7.07(4H, m), 7.15-7.22(1H, m), 8.48(1H,
s), 13.04(1H, s)
ESI/MS: 294[M+H]⁺, 316[M+Na]⁺
IR (KBr): 3156, 1679, 1575, 1475 cm⁻¹

25 Example 232

6-[2-Amino-4-(3-furyl)-5-pyrimidinyl]-3(2H)-
pyridazinone was prepared according to a similar manner to
that of Example 27.

¹H NMR (DMSO-d₆, δ): 6.51-6.52(1H, m), 6.84(1H, d, J=9.8 Hz),
30 6.94(2H, s), 7.26(1H, d, J=9.8 Hz), 7.71-7.78(2H, m), 8.26(1H,
s), 13.1(1H, s)
ESI/MS: 256[M+H]⁺, 278[M+Na]⁺

IR (KBr): 3187, 1658, 1581, 1490 cm^{-1}

Example 233

6-[2-Amino-4-(3-thienyl)-5-pyrimidinyl]-3(2H)-
pyridazinone was prepared according to a similar manner to
5 that of Example 27.

^1H NMR (DMSO- d_6 , δ): 6.76(1H, dd, $J=9.6, 2.2$ Hz), 6.98(2H, s),
7.03(1H, d, $J=9.6$ Hz), 7.13-7.16(1H, m), 7.55-7.59(1H, m),
7.62-7.64(1H, m), 8.31(1H, s), 13.11(1H, s)

ESI/MS: 272[M+H] $^+$, 294[M+Na] $^+$

10 IR (KBr): 3205, 1673, 1581, 1482 cm^{-1}

Example 234

6-[2-Amino-4-(2,6-dimethoxyphenyl)-5-pyrimidinyl]-
3(2H)-pyridazinone was prepared according to a similar manner
to that of Example 27.

15 ^1H NMR (DMSO- d_6 , δ): 3.60(6H, s), 6.60(1H, d, $J=10.8$ Hz), 6.66(2H,
d, $J=8.4$ Hz), 6.84(1H, d, $J=9.8$ Hz), 6.96(2H, s), 7.33(1H,
t, $J=8.4$ Hz), 8.35(1H, s), 12.95(1H, s)

ESI/MS: 326[M+H] $^+$, 340[M+Na] $^+$

IR (KBr): 3133, 1677, 1594, 1469 cm^{-1}

20 Example 235

6-[2-Amino-4-(4-bromophenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 1.01(6H, d, $J=6.6$ Hz), 4.96-5.10(1H, m),
25 6.85(1H, d, $J=9.6$ Hz), 7.12(2H, s), 7.28(1H, d, $J=9.6$ Hz),
7.28(2H, d, $J=8.8$ Hz), 7.58(2H, d, $J=8.8$ Hz), 8.47(1H, s),

ESI/MS: 384, 386[M+H] $^+$,

IR (KBr): 3397, 1646, 1581, 1481 cm^{-1}

mp: 204°C (aq-EtOH)

30 Example 236

6-[2-Amino-4-(3-bromophenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a

similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 0.99(6H, d, $J=6.6$ Hz), 4.96-5.09(1H, m), 6.87(1H, d, $J=9.6$ Hz), 7.16(2H, s), 7.25-7.34(2H, m), 7.35(2H, d, $J=9.6$ Hz), 7.55-7.61(2H, m), 8.49(1H, s),

5 ESI/MS: 384, 386[M+H] $^+$

IR (KBr): 3183, 1621, 1583, 1484 cm^{-1}

mp: 238-240°C (aq-EtOH)

Example 237

6-[2-Amino-4-(2,6-difluorophenyl)-5-pyrimidinyl]-
10 2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 0.82(6H, d, $J=6.6$ Hz), 4.86-4.99(1H, m), 6.92(1H, d, $J=9.6$ Hz), 7.09-7.19(2H, m), 7.23(2H, s), 7.40-7.55(1H, m), 8.62(1H, s)

15 ESI/MS: 366[M+Na] $^+$

mp: 244°C (aq-EtOH)

Example 238

6-[2-Amino-4-(3,5-difluorophenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
20 similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 0.99(6H, d, $J=6.6$ Hz), 4.96-5.10(1H, m), 6.91(1H, d, $J=9.6$ Hz), 7.01-7.06(2H, m), 7.20(2H, s), 7.24-7.35(1H, m), 7.43(1H, d, $J=9.6$ Hz), 8.53(1H, s)

ESI/MS: 344[M+H] $^+$, 366[M+Na] $^+$

25 IR (KBr): 3421, 1635, 1583, 1490 cm^{-1}

mp: 234°C (aq-EtOH)

Example 239

6-[2-Amino-4-(2,6-dichlorophenyl)-5-pyrimidinyl]-
2-isopropyl-3(2H)-pyridazinone was prepared according to a
30 similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 0.82(6H, d, $J=6.6$ Hz), 4.86-5.00(1H, m), 6.91(1H, d, $J=9.6$ Hz), 7.30-7.54(3H, m), 7.23(2H, s), 7.66(1H,

d, $J=9.6$ Hz), 8.67(1H, s)

ESI/MS: 376, 378[M+H]⁺, 398, 400[M+Na]⁺

IR (KBr): 3303, 1658, 1592, 1486 cm⁻¹

mp: 208°C (aq-EtOH)

5 Example 240

6-[2-Amino-4-(2,6-dimethylphenyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

¹H NMR (DMSO-d₆, δ): 0.92(6H, d, $J=6.6$ Hz), 1.94(6H, s), 4.97(1H, m), 6.78(1H, d, $J=9.6$ Hz), 7.00-7.17 (5H, m), 7.28(1H, d, $J=9.6$ Hz)

ESI/MS: 336[M+H]⁺, 358[M+Na]⁺, 693[2M+Na]⁺

IR (KBr): 3340, 1652, 1583, 1486 cm⁻¹

mp: 212°C (aq-EtOH)

15 Example 241

6-[2-Amino-4-(3-furyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

¹H NMR (DMSO-d₆, δ): 1.23(6H, d, $J=6.6$ Hz), 5.09-5.22(1H, m), 6.45(1H, s), 6.89(1H, d, $J=9.6$ Hz), 6.96(2H, s), 7.31(1H, d, $J=9.6$ Hz), 7.69-7.74(2H, m), 8.31(1H, s)

ESI/MS: 298[M+H]⁺, 320[M+Na]⁺

IR (KBr): 3160, 1650, 1591, 1489 cm⁻¹

mp: 216°C (aq-EtOH)

25 Example 242

6-[2-Amino-4-(3-thienyl)-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 27.

¹H NMR (DMSO-d₆, δ): 1.18(6H, d, $J=6.6$ Hz), 5.04-5.17(1H, m), 6.84(1H, d, $J=9.6$ Hz), 7.00(2H, s), 7.05-7.08(1H, m), 7.18(1H, d, $J=9.6$ Hz), 7.53-7.61(2H, m), 8.37(1H, s)

ESI/MS: 314[M+H]⁺, 336[M+Na]⁺

IR (KBr): 3189, 1675, 1581, 1482 cm^{-1}

mp: 234°C (aq-EtOH)

Example 243

6-[2-Amino-4-(2,6-dimethoxyphenyl)-5-pyrimidinyl]-
5 2-isopropyl-3(2H)-pyridazinone was prepared according to a
similar manner to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 0.99(6H, d, $J=6.6$ Hz), 3.57(6H, s), 4.97(1H,
m), 6.63(2H, d, $J=8.4$ Hz), 6.73(1H, d, $J=9.6$ Hz), 6.91(2H,
s), 7.15(1H, d, $J=9.6$ Hz), 7.27(1H, t, $J=8.4$ Hz), 8.40(1H,
10 s)

ESI/MS: 368[M+H] $^+$, 390[M+Na] $^+$

IR (KBr): 3409, 1648, 1581, 1486 cm^{-1}

mp: 260°C (aq-EtOH)

Example 244

15 6-[2-Amino-4-(3-furyl)-5-pyrimidinyl]-2-methyl-3(2H)-
pyridazinone was prepared according to a similar manner to
that of Example 27.

^1H NMR (DMSO- d_6 , δ): 3.69(3H, s), 6.54(1H, d, $J=9.6$ Hz), 6.88(1H,
d, $J=9.6$ Hz), 6.94(2H, s), 7.25(1H, d, $J=9.6$ Hz), 7.70-7.80(2H,
20 m), 8.26(1H, s)

ESI/MS: 292[M+Na] $^+$

IR (KBr): 3153, 1664, 1583, 1492 cm^{-1}

mp: 241°C (aq-EtOH)

Example 245

25 6-[2-Amino-4-(3-thienyl)-5-pyrimidinyl]-2-methyl-
3(2H)-pyridazinone was prepared according to a similar manner
to that of Example 27.

^1H NMR (DMSO- d_6 , δ): 3.69(3H, s), 6.80(1H, d, $J=9.6$ Hz), 7.04(2H,
s), 7.04(1H, d, $J=9.6$ Hz), 7.17-7.20(1H, m), 7.55-7.66(2H,
30 m), 8.31(1H, s)

ESI/MS: 286[M+H] $^+$, 308[M+Na] $^+$

IR (KBr): 3154, 1664, 1579, 1490 cm^{-1}

mp: 252°C (aq-EtOH)

Example 246

6-[2-Amino-4-(4-chlorophenyl)-5-pyrimidinyl]-3(2H)-pyridazinone (60 mg) was dissolved in N,N-dimethylformamide (5 ml). To the solution were added 60%-sodium hydride (28 mg) and methyl iodide (101 mg) at 25°C. The reaction mixture was heated at 50°C and stirred for 20 hours. The reaction mixture was added to a mixture of water and ethyl acetate. The organic layer was separated and washed with brine, and dried over magnesium sulfate. Evaporation of solvent in vacuo gave a residue. The residue was purified with chromatography on silica gel (methanol:chloroform 5:95 - 10:90), to give 6-[4-(4-chlorophenyl)-2-(dimethylamino)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone, which was crystallized from diisopropyl ether (30mg).

¹H NMR (DMSO-d₆, δ): 3.21(6H, s), 3.68(3H, s), 6.76(1H, d, J=9.6 Hz), 6.91(1H, d, J=9.6 Hz), 7.40-7.50(4H, m), 8.45(1H, s)

ESI/MS: 342, 344[M+H]⁺, 364, 366[M+Na]⁺

IR (KBr): 3354, 1674, 1580, 1480 cm⁻¹

mp: 166°C (IPE)

Example 247

6-[2-(Dimethylamino)-4-(4-methoxyphenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar manner to that of Example 246. ¹H NMR (DMSO-d₆, δ): 3.21(6H, s), 3.68(3H, s), 3.78(3H, s), 6.75(1H, d, J=9.6 Hz), 6.86(1H, d, J=9.6 Hz), 6.97(1H, d, J=8.8 Hz), 7.45(1H, d, J=8.8 Hz), 8.45(1H, s),

ESI/MS: 338[M+H]⁺, 360[M+Na]⁺

IR (KBr): 3354, 1653, 1563, 1485 cm⁻¹

mp: 165°C (IPE)

Example 248

6-[2-(Dimethylamino)-4-(3-fluorophenyl)-5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared according to a similar

manner to that of Example 246.

^1H NMR (DMSO- d_6 , δ): 3.21(6H, s), 3.68(3H, s), 6.75(1H, d, $J=9.6$ Hz), 6.93(1H, d, $J=9.6$ Hz), 7.16-7.45(3H, m), 8.45(1H, s)

ESI/MS: 326[M+H] $^+$, 348[M+Na] $^+$

5 IR (KBr): 3362, 1685, 1562, 1475 cm^{-1}

mp: 184°C (IPE)

Example 249

6-[2-(Dimethylamino)-4-(3-fluoro-4-methoxyphenyl)-
5-pyrimidinyl]-2-methyl-3(2H)-pyridazinone was prepared
10 according to a similar manner to that of Example 246.

^1H NMR (DMSO- d_6 , δ): 3.21(6H, s), 3.68(3H, s), 3.86(3H, s),
6.78(1H, d, $J=9.6$ Hz), 6.94(1H, d, $J=9.6$ Hz), 7.16-7.23(2H,
m), 7.42(1H, d, $J=14$ Hz), 8.45(1H, s)

ESI/MS: 356[M+H] $^+$, 378[M+Na] $^+$

15 IR (KBr): 3274, 1685, 1564, 1480 cm^{-1}

mp: 158°C (IPE)

Example 250

6-(2-Amino-4-phenyl-5-pyrimidinyl)-2-(2-methoxy-
1-methylethyl)-3(2H)-pyridazinone was obtained according to
20 a similar manner to that of Example 2.

mp: 180-181°C (EtOAc)

^1H NMR (DMSO- d_6 , δ): 1.00(3H, d, $J=6.8$ Hz), 3.16(3H, s),
3.19-3.44(2H, m), 5.11-5.21(1H, m), 6.79(1H, d, $J=9.6$ Hz),
7.08(2H, br s), 7.13(1H, d, $J=9.6$ Hz), 7.30-7.42(5H, m), 8.44(1H,
25 s)

Elemental Analysis for $\text{C}_{18}\text{H}_{19}\text{N}_5\text{O}_2$

Calcd.: C, 64.08; H, 5.68; N, 20.76

Found : C, 64.23; H, 5.67; N, 20.84

ESI/MS: 360[M+Na] $^+$

30 Example 251

To a stirred solution of
6-(2-amino-4-phenyl-5-pyrimidinyl)-2-(2-methoxy-

1-methylethyl)-3(2H)-pyridazinone (195 mg) in dichloromethane (4 ml) was added boron tribromide (0.273 ml) under ice cooling and the mixture was allowed to stir at 0°C - room temperature for 3.5h. The mixture was poured into ice-water, neutralized
5 with sat. NaHCO₃ and extracted with chloroform (x2). The combined extracts were washed with brine, dried over MgSO₄ and concentrated under reduced pressure to afford 168 mg of crystals. The crude material was purified by silica-gel column chromatography (CHCl₃-MeOH, 30:1) to give 129 mg of 6-(2-amino-4-phenyl-
10 5-pyrimidinyl)-2-(2-hydroxy-1-methylethyl)-3(2H)-pyridazinone as colorless crystals.

mp: 222-223°C (90% EtOH)

¹H NMR (DMSO-d₆, δ): 0.99(3H, d, J=6.8 Hz), 3.28-3.45(1H, m), 3.47-3.57(1H, m), 4.72(1H, t, J=5.8 Hz), 4.93-5.03(1H, m),
15 6.77(1H, d, J=9.6 Hz), 7.06(2H, s), 7.05(1H, d, J=9.6 Hz), 7.34-7.42(5H, m), 8.45(1H, s).

Elemental Analysis for C₁₇H₁₇N₅O₂

Calcd.: C, 63.15; H, 5.30; N, 21.66

Found : C, 63.23; H, 5.31; N, 21.69

20 APCI/MS: 324 [M+H]⁺

Example 252

A mixture of 6-(2-amino-6-oxo-4-phenyl-1,6-dihydro-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone (1.00 g), triethylamine hydrochloride (0.51 g) and phosphorous
25 oxychloride (1.44 ml) was heated at 100-105°C for 3 hours. After cooling, the mixture was poured into ice-water, neutralized with saturated sodium hydrogen carbonate solution, extracted with chloroform, dried over magnesium sulfate and concentrated under reduced pressure to give a residue. The residue was purified
30 by column chromatography on silica gel (ethyl acetate) to give 6-(2-amino-4-chloro-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (365 mg).
mp: 235-237°C (acetone)

IR (KBr): 3404, 3199, 1645, 1581, 1570 cm^{-1}

ESI/MS: 366 and 364 $[\text{M}+\text{Na}]^+$

^1H NMR (CDCl_3 , δ): 1.09 (6H, d, $J=6.60$ Hz), 5.22 (1H, 7-plet, $J=6.60$ Hz), 5.48 (2H, br.s), 6.83 (1H, d, $J=9.52$ Hz), 7.08 (1H, d, $J=9.52$ Hz), 7.26-7.35 (5H, m)

Example 253

To a mixture of 6-[2-amino-4-(methylsulfonyl)-6-phenyl-5-pyrimidinyl]-2-isopropyl-3(2H)-pyridazinone (386 mg) and [1,3-bis(diphenylphosphino)propane]dichloronickel(II) (56.9 mg) in tetrahydrofuran (10 ml) was dropwise added a 3 M solution of methyl magnesium bromide in tetrahydrofuran (1.7 ml) under an atmosphere of nitrogen. The mixture was stirred at atmosphere temperature for 20 hours and concentrated under reduced pressure to give a residue. The residue was dissolved in a mixture of aqueous ammonium chloride solution and chloroform. An organic layer was dried over magnesium sulfate, concentrated under reduced pressure and purified by column chromatography on silica gel (ethyl acetate) to give 6-(2-amino-4-methyl-6-phenyl-5-pyrimidinyl)-2-isopropyl-3(2H)-pyridazinone as a solid (66 mg).

mp: 213-215°C (methanol)

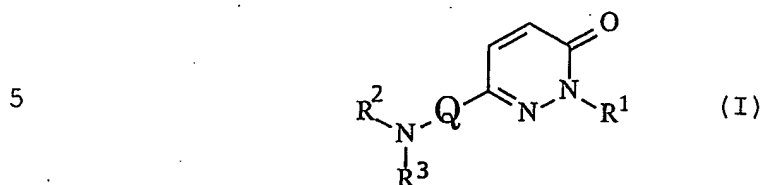
IR (KBr) : 3433, 3325, 3194, 1639, 1587, 1562 cm^{-1}

ESI/MS: 665 $[2\text{M}+\text{Na}]^+$, 344 $[\text{M}+\text{Na}]^+$, 322 $[\text{M}+\text{H}]^+$

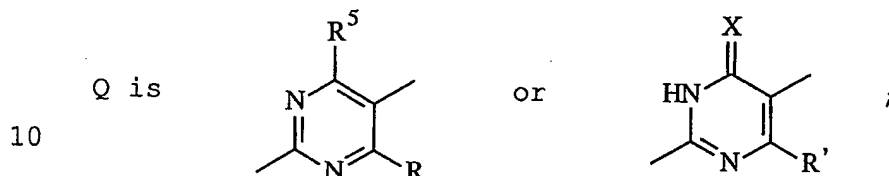
^1H NMR (CDCl_3 , δ): 1.28 (6H, d, $J=6.62$ Hz), 2.36 (3H, s), 5.21 (2H, br.s), 5.33 (1H, 7-plet, $J=6.62$ Hz), 6.70 (2H, s), 7.30 (5H, s)

CLAIMS

1. An aminopyrimidine compound of the following formula (I).



wherein



in which

R and R' are each optionally substituted aryl or heterocyclic group,

15 R⁵ is hydrogen, halogen, lower alkyl, optionally substituted hydroxy, optionally substituted amino which may form N-containing heterocyclic group, optionally substituted mercapto, lower alkylsulfinyl or lower alkylsulfonyl, and

20 X is oxygen or sulfur;

R¹ is hydrogen, optionally substituted lower alkyl or cyclo(lower)alkyl which may be interrupted by an oxygen atom;

R² and R³ are each independently

hydrogen, lower alkyl, acyl, aryl or heterocyclic(lower)alkyl,

25 R² and R³ may be combined together with N atom to which they are attached to form N-containing heterocyclic group; or a salt thereof.

2. A compound of claim 1,

30 wherein

R¹ is hydrogen, lower alkyl, hydroxy(lower)alkyl, lower alkoxy(lower)alkyl or phenyl(lower)alkyl,

R² is hydrogen, lower alkyl, lower alkanoyl or optionally

substituted benzoyl,

R^3 is hydrogen, lower alkyl, phenyl, pyridinyl(lower)alkyl or $-\text{CO}-R^{31}$,

in which R^{31} is lower alkyl, cyclo(lower)alkyl, lower alkoxy(lower)alkyl, optionally substituted lower alkoxy, optionally substituted phenyl or pyridinyl,

R^2 and R^3 may be combined together with N atom to which they are attached to form N-containing heterocyclic group;

R and R' are each

10



in which R^4 is hydrogen, halogen, hydroxy, lower alkyl, optionally substituted lower alkoxy, trihalo(lower)alkyl, loweralkylthio, lower alkylsulfinyl or lower alkylsulfonyl,

15

and n is an integer from 1 to 3,

provided R^4 may be different from each other when n is 2 or 3; and

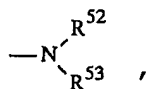
R^5 is hydrogen, halogen, lower alkyl, lower alkylthio, lower alkanoylthio, arylthio, lower alkylsulfinyl, lower alkylsulfonyl,

20

$-\text{O}-R^{51}$,

in which R^{51} is hydrogen, optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or

25



in which R^{52} is hydrogen or lower alkyl;

R^{53} is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group,

30

R^{52} and R^{53} may be combined together with N atom to which they are attached to form N-containing heterocyclic group.

3. A compound of claim 2,
wherein

R^1 is hydrogen, methyl, ethyl, propyl, isopropyl,
hydroxyisopropyl, methoxyisopropyl or benzyl;

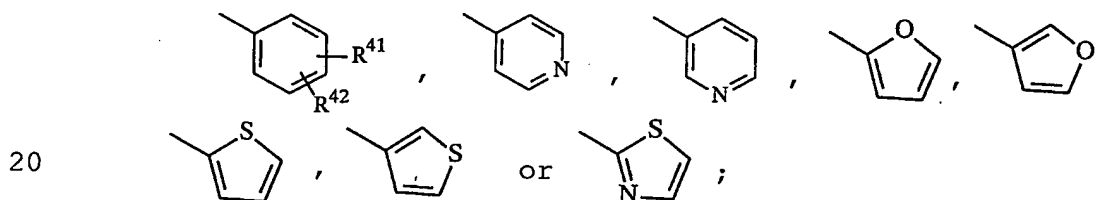
5 R^2 is hydrogen, methyl, acetyl, benzoyl, toluoyl, methoxybenzoyl,
trifluoromethylbenzoyl, fluorobenzoyl or chlorobenzoyl;

R^3 is hydrogen, methyl, phenyl, pyridinylmethyl or
-CO- R^{31} ,

10 in which R^{31} is methyl, propyl, isopropyl, isobutyl,
tert-butyl, cyclopropyl, cyclohexyl, methoxy,
methoxymethyl, trichloroethoxy, phenyl, tolyl,
methoxyphenyl, trifluoromethylphenyl, fluorophenyl,
chlorophenyl or pyridinyl, and

R^2 and R^3 may be combined together with N atom to which they
15 are attached to form morpholino;

R and R' are each

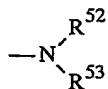


in which R^{41} and R^{42} are each independently hydrogen, fluoro,
bromo, chloro, hydroxy, methyl, trifluoromethyl, methoxy,
ethoxy, propoxy, isopropoxy, butoxy, isobutoxy,
25 isopentyloxy, hexyloxy, methoxyethoxy, fluoroethoxy,
fluoropropoxy, dimethylaminoethoxy, morpholinylethoxy,
methylthio, methylsulfinyl or methylsulfonyl; and

R^5 is hydrogen, fluoro, methyl, methylthio, acetylthio,
phenylthio, methylsulfinyl, methylsulfonyl,
30 -O- R^{51} ,

in which R^{51} is hydrogen, methyl, ethyl, propyl, isopropyl,
allyl, propynyl, cyclobutyl, cyclohexyl, hydroxyethyl,
methoxyethyl, carboxymethyl, aminoethyl,

dimethylaminoethyl, fluoroethyl, carbamoylmethyl,
 methylcarbamoylmethyl, dimethylcarbamoylmethyl,
 cyclopropylcarbamoylmethyl, methoxycarbonylmethyl,
 tert-butoxycarbonylmethyl, acetylmethyl, benzoylmethyl,
 5 phenyl, benzyl, pyridinylmethyl, pyridinylethyl,
 tetrahydro-2H-pyranyl or 1,3(2H)-dioxoisindolinylethyl,
 or



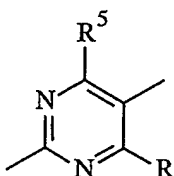
10 in which R^{52} is hydrogen or methyl,
 R^{53} is hydrogen, methyl, ethyl, propyl, isopropyl, tert-butyl,
 allyl, cyclopropyl, hydroxyethyl, methoxyethyl, aminoethyl,
 dimethylaminoethyl, carbamoylmethyl, amidino, phenyl,
 benzyl, pyridinyl, pyridinylmethyl, furylmethyl or
 15 dimethylthiazolyl,
 R^{52} and R^{53} may be combined together with N atom to which
 they are attached to form pyrrolidinyl, piperidinyl,
 morpholino, piperazinyl, methylpiperazinyl, imidazolyl,
 triazolyl or benzimidazolyl.

20

4. A compound of claim 1,
 wherein

Q is

25



in which R and R^5 are each as defined in claim , and
 R^1 is optionally substituted lower alkyl.

30 5. A compound of claim 4,
 wherein

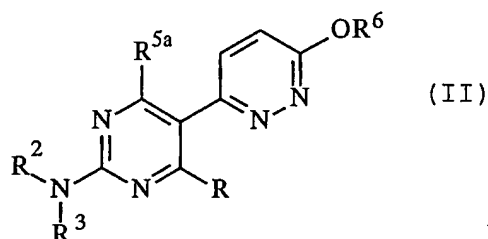
R^1 is lower alkyl or lower alkoxy(lower)alkyl, and
 R^5 is hydrogen.

6. A compound of claim 5,
 wherein
 R^1 is lower alkyl, and
 R^2 is hydrogen.

5

7. A process for the preparation of the aminopyrimidine compound
 of claim 1 or a salt thereof, which comprises,
 (1) hydrolyzing a compound of the formula (II):

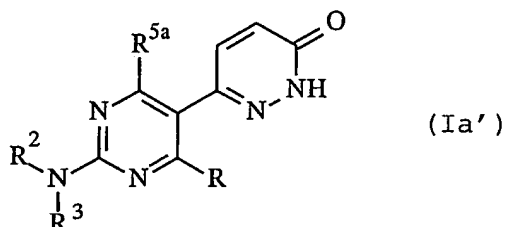
10



wherein

15 R , R^2 and R^3 are each as defined above,
 R^{5a} is hydrogen, lower alkyl, optionally substituted hydroxy
 or optionally substituted amino, and
 R^6 is lower alkyl, or a salt thereof,
 to give a compound of the formula (Ia'):

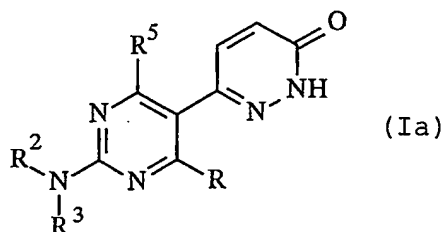
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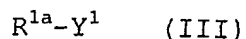
25 wherein R , R^2 , R^3 and R^{5a} are each as defined above or a salt
 thereof,

(2) reacting a compound of the formula (Ia):

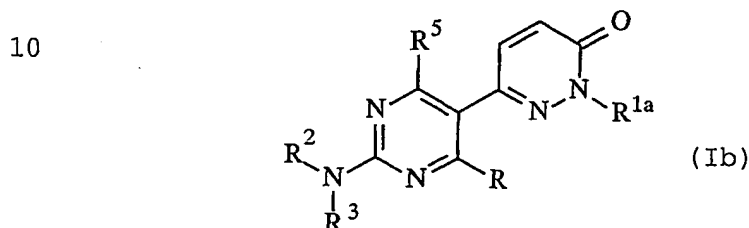
30



wherein R, R², R³ and R⁵ are each as defined above or a salt thereof, with a compound of the formula (III):

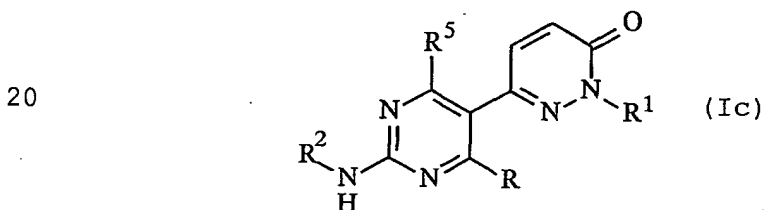


wherein R^{1a} is lower alkyl, cyclo(lower)alkyl which may be interrupted by an oxygen atom or aryl(lower)alkyl, and Y¹ is a leaving group, or a salt thereof, to give a compound of the formula (Ib):

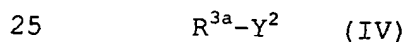


15 wherein R, R², R³, R⁵ and R^{1a} are each as defined above or a salt thereof,

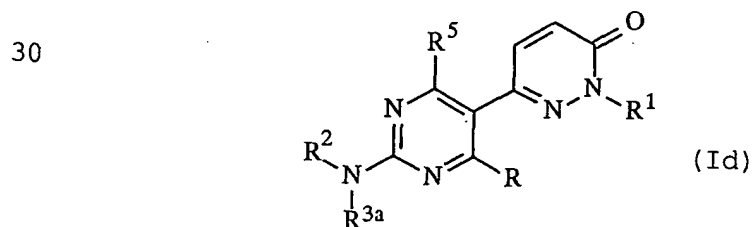
(3) reacting a compound of the formula (Ic):



wherein R, R¹, R² and R⁵ are each as defined above or a salt thereof, with a compound of the formula (IV):



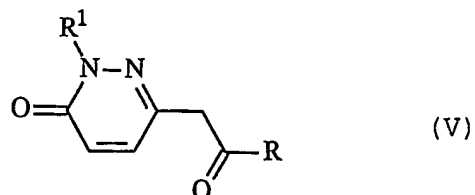
wherein R^{3a} is lower alkyl, acyl, aryl and aryl(lower)aryl, and Y² is a leaving group, or a salt thereof to give a compound of the formula (Id):



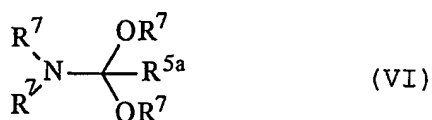
wherein R, R¹, R², R⁵ and R^{3a} are each as defined above or a salt thereof,

(4) reacting a compound of the formula (V):

5

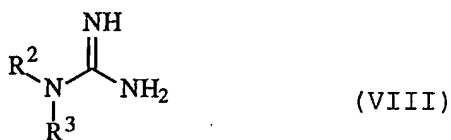


wherein R and R¹ are each as defined above or a salt thereof,
10 with a compound of the formula:



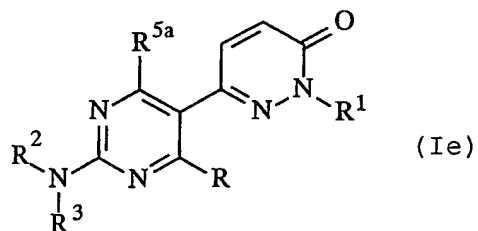
wherein R^{5a} is as defined above,
15 and R⁷ is lower alkyl or a salt thereof,
and further with a compound of the formula (VIII):

20



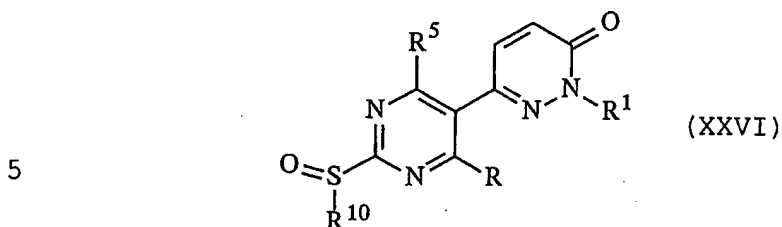
wherein R² and R³ are each as defined above or a salt thereof,
to give a compound of the formula (Ie):

25



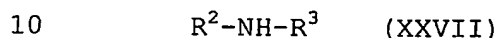
wherein R, R¹, R², R³ and R^{5a} are each as defined above or a
30 salt thereof,

(5) reacting a compound of the formula (XXVI):

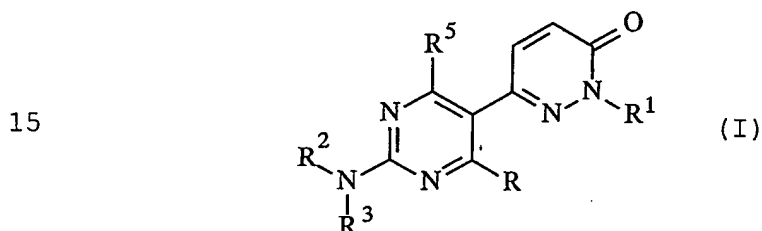


wherein R, R¹ and R⁵ are each as defined above, and
R¹⁰ is lower alkyl, or a salt thereof,

with a compound of the formula (XXVII):

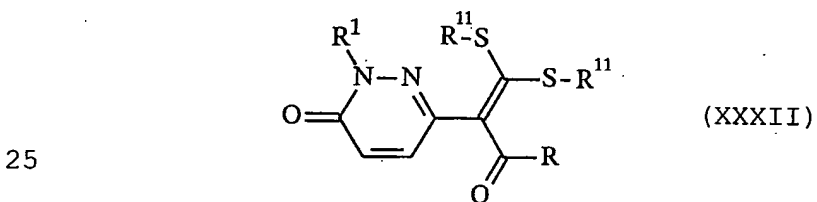


wherein R² and R³ are each as defined above or a salt thereof,
to give a compound of the formula (I):

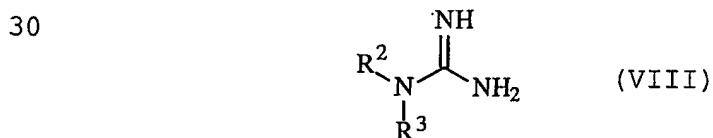


wherein R, R¹, R², R³ and R⁵ are each as defined above or a salt
thereof,

(6) reacting a compound of the formula (XXXII):

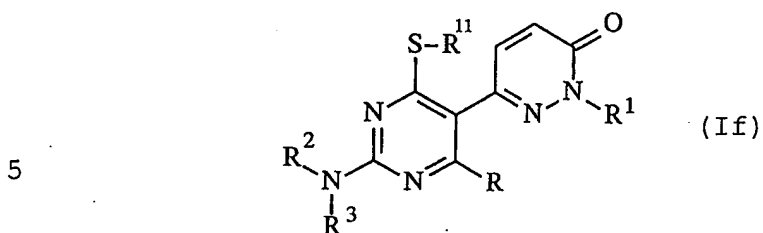


wherein R and R¹ are each as defined above, and
R¹¹ is lower alkyl, or a salt thereof,
with a compound of the formula (VIII):



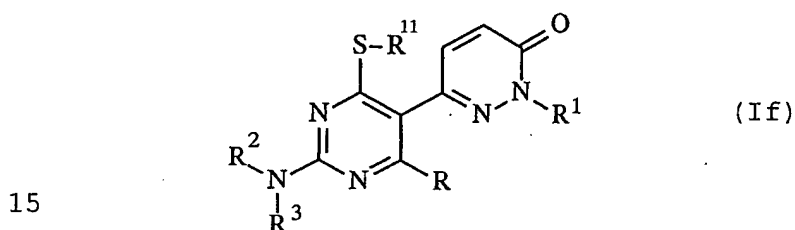
wherein R² and R³ are each as defined above or a salt thereof,

to give a compound of the formula (If):



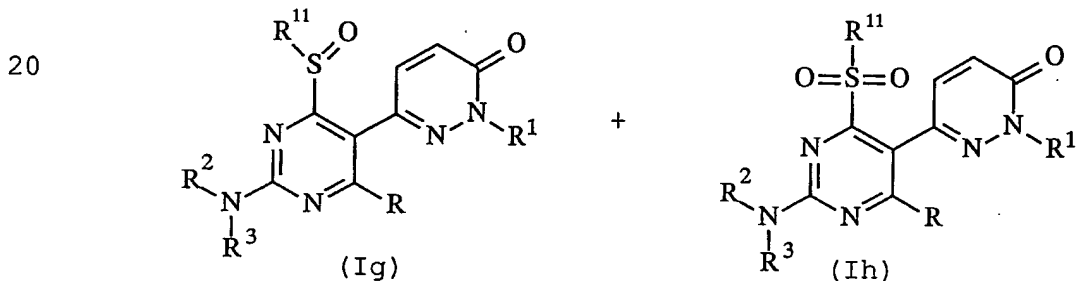
wherein R, R¹, R², R³ and R¹¹ are each as defined above or a salt thereof,

10 (7) oxidizing a compound of the formula (If):



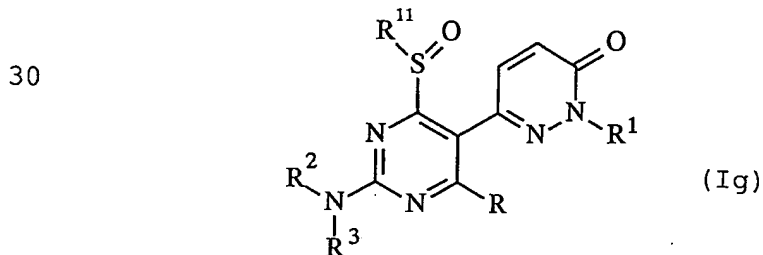
wherein R, R¹, R², R³ and R¹¹ are each as defined above or a salt thereof,

to give compounds of the formula (Ig) and (Ih):



25 wherein R, R¹, R², R³ and R¹¹ are each as defined above or a salt thereof,

(8) reacting a compound of the formula (Ig):



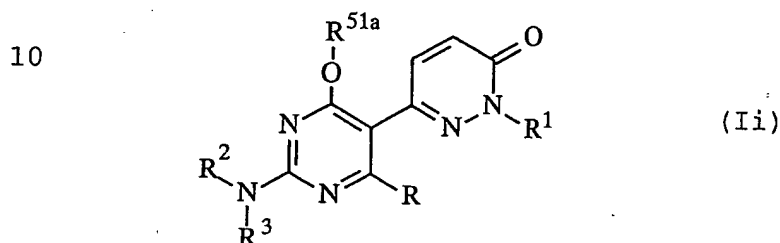
wherein R, R¹, R², R³ and R¹¹ are each as defined above or a salt thereof,

with a compound of the formula (XXXIII):



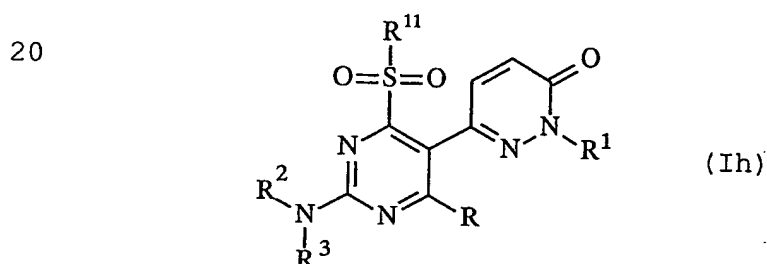
- 5 wherein R^{51a} is optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group, or a salt thereof,

to give a compound of the formula (Ii):



- 15 wherein R, R¹, R², R³ and R^{51a} are each as defined above or a salt thereof,

(9) reacting a compound of the formula (Ih):



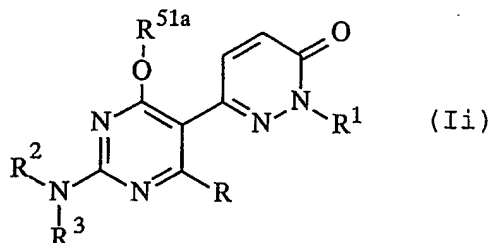
- 25 wherein R, R¹, R², R³ and R¹¹ are each as defined above or a salt thereof,

with a compound of the formula (XXXIII):



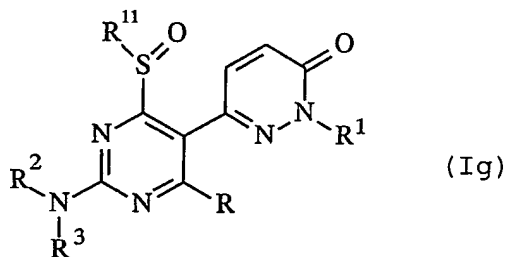
- wherein R^{51a} is optionally substituted lower alkyl, lower alkenyl, lower alkynyl, cyclo(lower)alkyl, aryl or heterocyclic group,
- 30 or a salt thereof,

to give a compound of the formula (Ii):



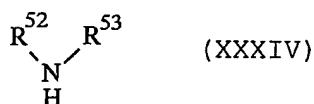
wherein R, R¹, R², R³ and R^{51a} are each as defined above or a salt thereof,

(10) reacting a compound of the formula (Ig):



wherein R, R¹, R², R³ and R¹¹ are each as defined above or a salt thereof,

with a compound of the formula (XXXIV):

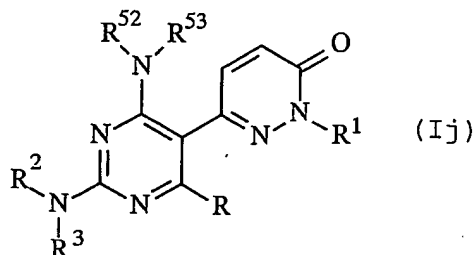


wherein R⁵² is hydrogen or lower alkyl,

R⁵³ is hydrogen, optionally substituted lower alkyl, lower alkenyl, cyclo(lower)alkyl, amidino, aryl or heterocyclic group, and

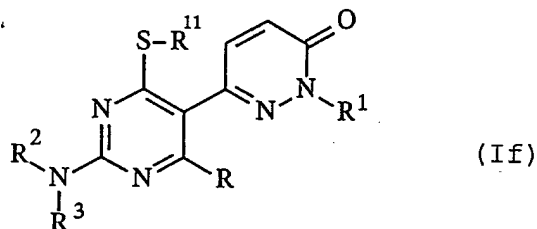
25 R⁵² and R⁵³ may be combined together with N atom to which they are attached to form N-containing heterocyclic group, or a salt thereof,

to give a compound of the formula (Ij):



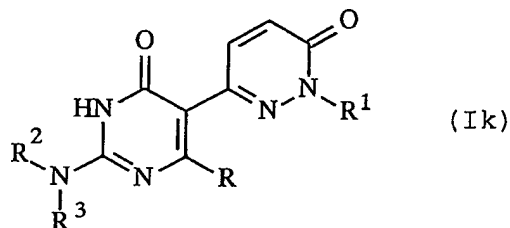
wherein R , R^1 , R^2 , R^3 , R^{52} and R^{53} are each as defined above or a salt thereof,

(11) reacting a compound of the formula (If):



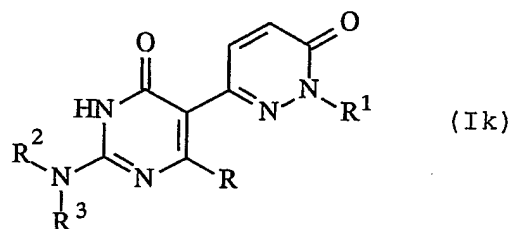
10 wherein R , R^1 , R^2 , R^3 and R^{11} are each as defined above or a salt thereof,

with urea hydrogen peroxide addition compound,
to give a compound of the formula (Ik):



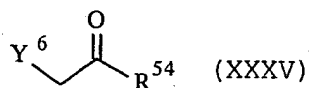
20 wherein R , R^1 , R^2 and R^3 are each as defined above or a salt thereof,

(12) reacting a compound of the formula (Ik):

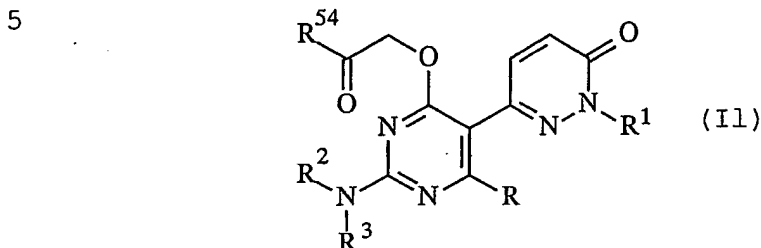


30 wherein R , R^1 , R^2 and R^3 are each as defined above or a salt thereof,

with a compound of the formula (XXXV):



wherein R^{54} is lower alkyl, cyclo(lower)alkyl, lower alkoxy or aryl, and Y^6 is a leaving group, or a salt thereof, to give a compound of the formula (II):

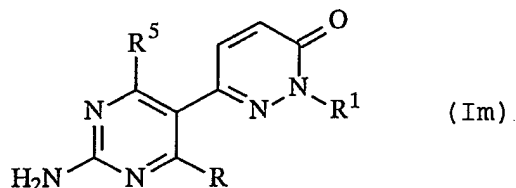


10

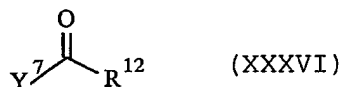
wherein R , R^1 , R^2 , R^3 and R^{54} are each as defined above or a salt thereof,

(13) reacting a compound of the formula (Im):

15

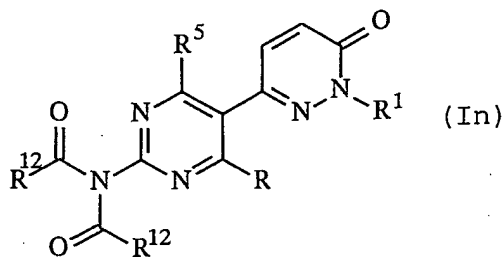


20 wherein R , R^1 and R^5 are each as defined above or a salt thereof, with a compound of the formula (XXXVI):



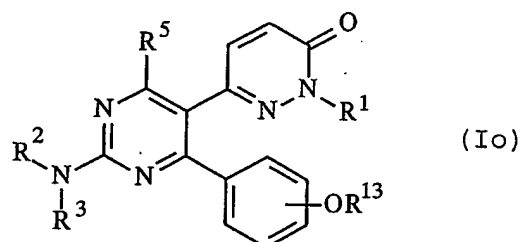
wherein R^{12} is optionally substituted aryl or lower alkoxy, and Y^7 is a leaving group, or a salt thereof, to give a compound of the formula (In):

30

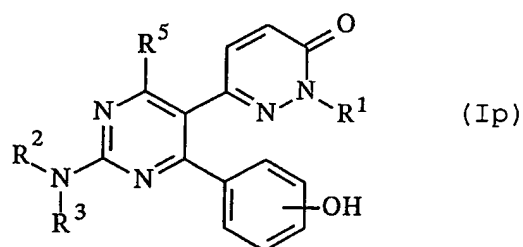


wherein R, R¹, R², R³ and R⁵⁴ are each as defined above or a salt thereof,

(14) reacting a compound of the formula (Io):

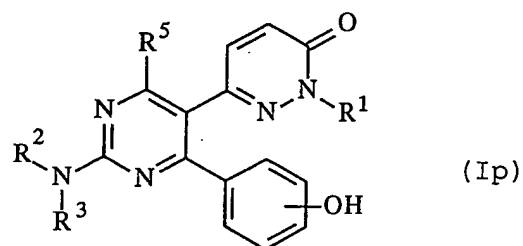


wherein R¹, R², R³ and R⁵ are each as defined above, and R¹³ is lower alkyl, or a salt thereof, to give a compound of the formula (Ip):



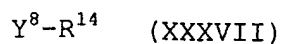
20 wherein R¹, R², R³ and R⁵ are each as defined above or a salt thereof,

(15) reacting a compound of the formula (Ip):



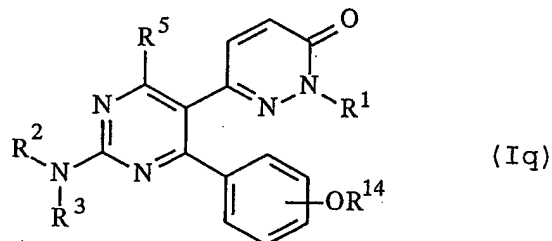
30 wherein R¹, R², R³ and R⁵ are each as defined above, or a salt thereof,

with a compound of the formula (XXXVII):



wherein R^{14} is optionally substituted lower alkyl, and Y^8 is a leaving group, or a salt thereof, to give a compound of the formula (Iq):

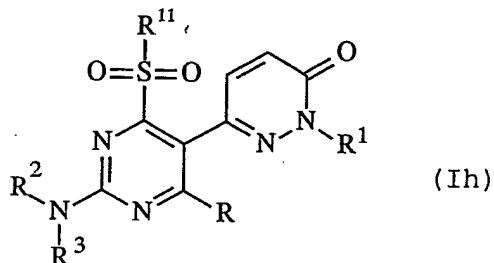
5



10 wherein R^1 , R^2 , R^3 , R^5 and R^{14} are each as defined above or a salt thereof.

(16) reacting a compound of the formula (Ih):

15



20 wherein R , R^1 , R^2 , R^3 and R^{11} are each as defined above, or a salt thereof,

with a compound of the formula (XXXVIII):

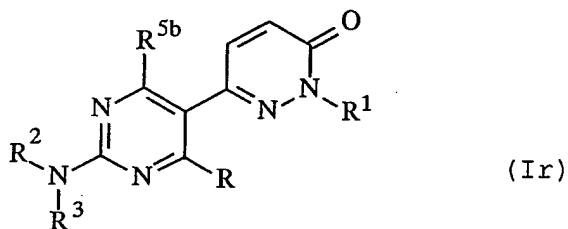


wherein R^{5b} is lower alkyl, Y^9 is a leaving group and M is metal,

25 or a salt thereof,

to give a compound of the formula (Ir):

30



wherein R , R^1 , R^2 , R^3 and R^{5b} are each as defined above or a salt thereof.

8. A pharmaceutical composition comprising the compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable carrier.
- 5 9. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, heart failure, hypertension, circulatory insufficiency, post-resuscitation, asystole, bradyarrhythmia, electro-mechanical dissociation, hemodynamic collapse, SIRS (systemic inflammatory response syndrome), multiple organ failure, renal failure (renal insufficiency), renal toxicity, nephrosis, nephritis, edema, obesity, bronchial asthma, gout, hyperuricemia, sudden infant death syndrome, immunosuppression, diabetes, ulcer, 10 pancreatitis, Meniere's syndrome, anemia, dialysis-induced hypotension, constipation, ischemic bowel disease, ileus, myocardial infarction, thrombosis, obstruction, arteriosclerosis obliterans, thrombophlebitis, cerebral infarction, transient ischemic attack and angina pectoris, 15 which comprises administering the compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.
- 20 10. A method for preventing or treating a disease selected from the group consisting of depression, dementia, Parkinson's disease, anxiety, pain, cerebrovascular disease, Meniere's syndrome and cerebral infarction, which comprises administering the compound of claim 1 or a pharmaceutically acceptable salt thereof to a human being or an animal.
- 25 30 11. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as a medicament.

12. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an adenosine antagonist.
13. A compound of claim 1 or a pharmaceutically acceptable salt thereof for use as an A₁ receptor and A₂ receptor dual antagonist.
14. A process for preparing a pharmaceutical composition which comprises admixing the compound of claim 1 or a pharmaceutically acceptable salt thereof with a pharmaceutically acceptable carrier.
15. Use of the compound of claim 1 or a pharmaceutically acceptable salt thereof for the production of a pharmaceutical composition for the therapy of diseases on which an adenosine antagonist is therapeutically effective.
16. A method for evaluation of adenosine antagonism which comprises use of compound of claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/13796

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D403/04 C07D409/14 C07D401/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 848 000 A (TANABE SEIYAKU CO) 17 June 1998 (1998-06-17) claims 1,19,20; examples 21,34 ---	1,8,9
A	EP 0 748 805 A (TANABE SEIYAKU CO) 18 December 1996 (1996-12-18) claims 1,37,38; example 49 ---	1,8,9
A	WO 91 12251 A (CHUGAI PHARMACEUTICAL CO LTD) 22 August 1991 (1991-08-22) abstract; claims 1,3 ---	1,8,9
A	PATENT ABSTRACTS OF JAPAN vol. 2000, no. 05, 14 September 2000 (2000-09-14) -& JP 2000 063275 A (TANABE SEIYAKU CO LTD), 29 February 2000 (2000-02-29) abstract; example 21 ---	1,8,9
-/--		

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

Date of the actual completion of the international search

20 May 2003

Date of mailing of the international search report

28/05/2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
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Authorized officer

Hass, C

INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 02/13796

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>PATENT ABSTRACTS OF JAPAN vol. 1998, no. 13, 30 November 1998 (1998-11-30) -& JP 10 226647 A (TANABE SEIYAKU CO LTD), 25 August 1998 (1998-08-25) abstract; example 49</p>	1,8,9
A	<p>M. YAMAGUCHI ET AL: "Novel Antiasthmatic Agents with Dual Activities of Thromboxane A2 Synthetase Inhibition and Bronchodilation. 2. 4-(3-Pyridyl)- 1(2H)-phthalazinones" JOURNAL OF MEDICINAL CHEMISTRY, vol. 36, no. 25, 1993, pages 4061-4068, XP001151968 table I</p>	1,9

INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP 02/13796

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 9, 10 and possibly 16 are directed to a method of treatment or a diagnostic method of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 02/13796

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
EP 0848000	A	17-06-1998	AT 219075 T	15-06-2002
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			CN 1184813 A	17-06-1998
			DE 69713255 D1	18-07-2002
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			DE 69600221 T2	06-08-1998
			EP 0748805 A1	18-12-1996
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			ZA 9604652 A	12-12-1996
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			WO 9112251 A1	22-08-1991
			JP 3120857 B2	25-12-2000
			ZA 9101224 A	27-11-1991
JP 2000063275	A	29-02-2000	NONE	
JP 10226647 5	A		NONE	

ABSTRACT

The present invention concerns chemical compounds combining affinity and antagonism against the human m3 muscarinic receptor with activity as selective phosphodiesterase IV (PDE IV) inhibitors, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

CLAIMS**WO03087064**

Claims: 1. A compound having the formula I, or a pharmaceutically acceptable salt thereof,

EMI61.1

wherein Y is -NH-R2 or a group of formula

EMI61.2

RI is cycloalkyl or non-substituted alkyl, R2 is cycloalkyl, R3 is hydrogen, alkyl, halogen, hydroxy, alkoxy or amino, or R2R3 is an alkylene bridging group, Ra is hydrogen, alkyl, alkenyl, alkynyl, halogen, hydroxy, alkoxy, amino, alkylamino, alkylsulfonyloxy, cyano, carboxy, ester or amido, Rb is hydrogen, alkyl or halogen, or RaRb is carbonyl, R4 is hydrogen or alkyl, R5 is cycloalkyl, arylalkyl or heterocycle-alkyl, or NR4R5 is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom, with the proviso that when Y is -NHR2 and R2R3 is an alkylene bridging group or when Y is a group of formula

EMI61.3

RI is a cycloalkyl.

2. A compound according to claim 1 wherein Y is -NH-R2.

<Desc/Clms Page number 62>

3. A compound according to claim 2 wherein

RI is C3-7-cycloalkyl or non-substituted alkyl,

R2 is C3-7-cycloalkyl,

R3 is hydrogen, C1-4-alkyl, halogen, hydroxy, alkoxy or amino, or R2R3 is a C2-4-alkylene bridging group, R4 is hydrogen or C1-4-alkyl, R5 is C3-7-cycloalkyl, arylalkyl or heterocycle-alkyl, or NR4R5 is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom.

4. A compound according to claim 2 or 3 wherein RI is C3-4-alkyl or C3-5- cycloalkyl, preferably cyclopropyl, isopropyl, cyclobutyl, cyclopentyl, 2-methyl- cyclopropyl or cyclopropylmethyl.

5. A compound according to any of claims 2 to 4 wherein

R2 is a C3-4-non-substituted cycloalkyl, or a cycloalkyl substituted by a C1-6- alkyl or an aryl, preferably cyclopropyl or cyclobutyl, and/or R3 is hydrogen, methyl, ethyl, a Cl atom, a F atom, a Br atom, amino or methoxy, or R2R3 is an alkylene bridging group selected from ethylene, propylene and butylene.

6. A compound according to any of claims 2 to 5 wherein R4 is hydrogen or C 1-4-alkyl, preferably hydrogen or methyl, and/or R5 is 2- (2-thienyl) ethyl, 2-furylmethyl, 2-thienylmethyl, 4- pyridinylmethyl,

benzyl, 2- (methylsulfanyl) benzyl, 2, 6-difluorobenzyl, 2- fluorobenzyl, 2-nitrobenzyl, 3,5-bis (trifluoromethyl) benzyl, 3, 5-difluorobenzyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, or 2,2-diphenylethyl, or NR4R5 is 1, 3-thiazolidin-3-yl, 1-azepanyl, 1-azocanyl, 3,5-dimethyl-1- piperidinyl, 4- (2-methoxyphenyl)-1-piperidinyl, 4-(hydroxydiphenyl) methyl)-1- piperidinyl, 4- (trifluoromethyl)-1-piperidinyl, 4, 4-difluoro-1-piperidinyl, 4,4-dimethyl-1-piperidinyl, 4-carbamoyl-1-piperidinyl, 4-benzyl-1-piperidinyl, 4-

piperidinyl, 4-hydroxy-4-phenyl-1-piperidinyl, 4-hydroxymethyl-1-piperidinyl, 4-methyl-1-piperidinyl, 4-methylene-1-piperidinyl, 4-oxo-1-piperidinyl, 3,6-dihydro-1 (2H)-pyridinyl, 3-azabicyclo [3.2.1] oct-3-yl, 4-thiomorpholinyl, 2-one-1-azepanyl, 3, 4-dihydro-2(1H)-isoquinolinyl, 1,4-dioxa-8-azaspiro [4. 5] dec-8-yl, 1, 3,3-trimethyl-6-azabicyclo [3.2. 1]oct-6-yl, octahydro-2(1H)-isoquinolinyl or 8- azaspiro [4.5]dec-8-yl.

7. A compound selected from 6- (1-azepanyl)-N, 2-dicyclopropyl-5-methyl-4- pyrimidinamine ; N, 2-dicyclopropyl-6- (4, 4-dimethyl-1-piperidinyl)-5-methyl-4- pyrimidinamine; N, 2-dicyclopropyl-5-methyl-6- (4-methyl-1-piperidinyl)-4- pyrimidinamine ; 6- (3-azabicyclo [3.2. 1] oct-3-yl)-N, 2-dicyclopropyl-5-methyl-4- pyrimidinamine; N, 2-dicyclopropyl-5-methyl-6- (4-thiomorpholinyl)-4-pyrimidinamine; 4-azepan-1-yl-2-cyclopropyl-5, 6,7, 8-tetrahydro-pyrido[2, 3- d] pyrimidine and 4-azepan-1-yl-2-cyclopropyl-6, 7,8, 9-tetrahydro-pyrimido [4,5- b] azepine, or pharmaceutically acceptable salts thereof.

8. A compound according to claim I wherein Y is a group of formula EMI63.1

9. A compound according to claim 8 wherein NR4R5 is a 5-to 9-membered heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom, preferably 1-azepanyl.

10. A compound according to claim 9 wherein

RI is C3-7-cycloalkyl,

R3 is hydrogen, C1-4-alkyl, halogen, hydroxy, alkoxy or amino,

Ra is hydrogen, C 1-4-alkyl, C2-6-alkenyl, C2-6-alkynyl, halogen, hydroxy, alkoxy, amino, alkylamino, alkylsulfonyloxy, cyano, carboxy, ester or amido, Rb is hydrogen, C 1-4-alkyl or halogen, or RaRb is carbonyl.

11. A compound according to any of claims 8 to 10 wherein RI is C3-4-cycloalkyl, preferably cyclopropyl.

12. A compound according to any of claims 8 to 11 wherein R3 is hydrogen or C1-4-alkyl, preferably hydrogen or methyl.

13. A compound according to any of claims 8 to 12 wherein

Ra is hydrogen, methyl, hydroxy, methoxy, methylsulfonyloxy, a Br atom, a F atom or cyano, preferably, hydrogen, methyl, hydroxy or a F atom, and/or Rb is hydrogen or methyl, preferably hydrogen, or RaRb is carbonyl.

14. A compound selected from 1-(6-azetidin-1-yl-2-cyclopropyl-5-methylpyrimidin-

4-yl) azepane and 1-[2-cyclopropyl-5-methyl-6-(3-methylazetidin-1-yl) pyrimidin-4-yl] azepane, or pharmaceutically acceptable salts thereof.

15. A compound according to any preceding claims as a pure enantiomer.
16. A pharmaceutical composition comprising an effective amount of a compound according to any preceding claim in combination with a pharmaceutically acceptable diluent or carrier.
17. A pharmaceutical composition according to claim 16 for administration by inhalation.
18. A compound according to any of claims 1-15 or a pharmaceutically acceptable salt thereof for use as a medicament.
19. The use of a compound according to any of claims 1-15 for the manufacture of a medicament for the treatment of respiratory disorders in connection with Chronic Obstructive Pulmonary Disease or for treatment of symptoms related to chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis or asthma.
20. A method for treating respiratory disorders in connection with Chronic Obstructive Pulmonary Disease or for treating symptoms related to chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis or asthma comprising administering at least one compound according to claims 1-15 or a pharmaceutically acceptable salt thereof to a patient.

A compound of formula II, or a pharmaceutically acceptable salt thereof,

EMI65.1

wherein Y is -NH-R or a group of formula

EMI65.2

R₁ is cycloalkyl or non-substituted alkyl, R₂ is cycloalkyl, R₃ is hydrogen, alkyl, halogen, alkoxy or hydroxy, R_a is hydrogen, alkyl, alkenyl, alkynyl, halogen, hydroxy, alkoxy, amino, alkylamino, alkylsulfonyloxy, cyano, carboxy, ester or amido, R_b is hydrogen, alkyl or halogen, or R_aR_b is carbonyl.

A compound of formula VI, or a pharmaceutically acceptable salt thereof,

EMI65.3

wherein R₁ is C₃-5-cycloalkyl or non-substituted alkyl, and R₃ is alkoxy.

A compound of formula X, or a pharmaceutically acceptable salt thereof,

EMI65.4

wherein n is 1-6, and R₁ is cycloalkyl.

A compound of formula XII, or a pharmaceutically acceptable salt thereof,

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EMI66.1

wherein RI is cycloalkyl.

25. A compound selected from the group consisting of 6-chloro-N, 2-dicyclopropyl-5-fluoro-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; 5, 6-dichloro-N, 2-dicyclopropyl-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-methoxy-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-ethyl-4-pyrimidinamine ; N-16-chloro-2-(2-trans-methylcyclopropyl)-4-pyrimidinyl-N-cyclopropylamine and its enantiomers; 6-chloro-N-cyclopropyl-5-methyl-2-(2-trans-methylcyclopropyl)-4-pyrimidinamine ; 6-chloro-N-cyclopropyl-5-methyl-2-[2-cis-methylcyclopropyl]-4-pyrimidinamine ; N-[6-chloro-2-(cyclopropylmethyl)-5-methyl-4-pyrimidinyl]-N-cyclopropylamine; 6-chloro-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-nitro-4-pyrimidinamine ; 6-chloro-N-cyclobutyl-2-cyclopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-N-cyclopropyl-2-isopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-2-cyclopentyl-N-cyclopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-2-cyclopropyl-5-methyl-N-(2-methylcyclopropyl)-4-pyrimidinamine ; 6-chloro-2-cyclopropyl-5-methyl-N-(1-methylcyclopropyl)-4-pyrimidinamine ; 6-chloro-2-cyclopropyl-5-methyl-N-(2-phenylcyclopropyl)-4-pyrimidinamine ; 4-(1-azetidynyl)-6-chloro-2-cyclopropyl-5-methylpyrimidine ; 4-(1-azetidynyl)-6-chloro-2-cyclopropyl-5-methylpyrimidine ; 4-chloro-2-cyclopropyl-5-methyl-6-(3-methyl-1-azetidynyl)pyrimidine ; 4-chloro-2-cyclopropyl-6-(3-methyl-1-azetidynyl)pyrimidine ; 4-chloro-2-cyclopropyl-6-(3-fluoro-1-azetidynyl)-5-methylpyrimidine ; 4-chloro-2-cyclopropyl-6-(3-methoxy-1-azetidynyl)-5-methylpyrimidine ; 2-methylcyclopropanecarboximidamide ; 2-cyclopropyl-5-fluoro-4, 6-pyrimidinediol ; 5-chloro-2-cyclopropyl-4,6-pyrimidinediol ; 2-cyclopropyl-5-methoxy-4,6-pyrimidinediol ; 2-cyclopropyl-5-ethyl-4,6-pyrimidinediol ; 2-(2-methylcyclopropyl)-4,6-pyrimidinediol ; 5-methyl-2-(2-methylcyclopropyl)-4,6-pyrimidinediol ; 2-(cyclopropylmethyl)-5-methyl-4,6-pyrimidinediol ; 2-cyclobutyl-5-methyl-4,6-pyrimidinediol ; 2-isopropyl-5-methyl-4,6-pyrimidinediol ; 2-cyclopentyl-5-methyl-4,6-pyrimidinediol ; [3-(2-cyclopropyl-

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4, 6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester; [4-(2-cyclopropyl-4,6-dihydroxy-pyrimidin-5-yl)-butyl]-carbamic acid tert-butyl ester; 4, 6-dichloro-2-cyclopropyl-5-fluoropyrimidine ; 4,5,6-trichloro-2-cyclopropylpyrimidine ; 4,6-dichloro-2-cyclopropyl-5-pyrimidinyl methyl ether; 4,6-dichloro-2-cyclopropyl-5-ethylpyrimidine ; 4,6-dichloro-2-(2-methylcyclopropyl)pyrimidine ; 4,6-dichloro-5-methyl-2-(2-methylcyclopropyl)pyrimidine; 4, 6-dichloro-2-(cyclopropylmethyl)-5-methylpyrimidine ; 4,6-dichloro-2-cyclobutyl-5-methylpyrimidine ; 4,6-dichloro-2-isopropyl-5-methylpyrimidine ; 4,6-dichloro-2-cyclopentyl-5-methylpyrimidine ; 6-(1-azepanyl)-N, 2-dicyclopropyl-5-nitro-4-pyrimidinamine ; 4-chloro-2-cyclopropyl-6,7-dihydro-5H-pyrrolo [2,3-d] pyrimidine ; 4-chloro-2-cyclopropyl-5,6, 7, 8-tetrahydro-5H-pyrido [2, 3-d] pyrimidine ; 4-chloro-2-cyclopropyl-6, 7,8, 9-tetrahydro-5H-pyrimido [4,5-b] azepine ; 2-cyclopropyl-6,7-dihydro-5H-pyrrolo [2,3-d]pyrimidin-4-ol ; 3-fluoroazetidine hydrochloride and 1-benzhydryl-3-fluoroazetidine.

DESCRIPTION

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<Desc/Clms Page number 1>

Chemical Compounds with Dual Activity, processes for their preparation and pharmaceutical compositions

The present invention concerns chemical compounds combining affinity and antagonism against the human m3 muscarinic receptor with activity as selective phosphodiesterase IV (PDE IV) inhibitors, processes for preparing them, pharmaceutical compositions containing them and their use as pharmaceuticals.

Chronic obstructive pulmonary disease is characterised by airway inflammation and impaired expiratory outflow due to chronic bronchitis and/or emphysema. The primary inflammatory cells associated with COPD are macrophages, CD8+ T-cells and neutrophils.

Parasympathetic cholinergic reflexes are the most potent tonically active regulators of bronchoconstriction and of submucosal gland exocytosis and secretion in the airways. Post-junctional m3 receptors mediate cholinergic bronchoconstriction and glandular secretion in the human airways. Prejunctional m2 autoreceptors modulate the acetylcholine release whereas m1 receptors located on parasympathetic ganglia inversely facilitate the parasympathetic nerve activity (Barnes P. J., In: "Lung Biology in Health and Disease: Anticholinergic Agents in the Upper and Lower Airways", Vol. 134, Spector S. L. (Ed), (1999), 31-57).

The nasal mucosa of the upper airway is also innervated by parasympathetic nerve fibers, activation of which results in glandular hypersecretion from both goblet cells and submucosal seromucinous glands. Activation of m1 and m3 receptors results in secretion from mucous and serous glands. The m3 receptor subtype, also present on blood vessels, may play an additional role in nasal congestion through promoting vasodilatation.

Thereby, M3 and M1 muscarinic receptor antagonists are indicated for the treatment of diseases associated with airway narrowing or/and mucus hypersecretion (Morley, J. Parasympatholytics in Asthma. Pulmonary Pharmacology (1994), 7, 159- 168).

Anticholinergic bronchodilators, particularly selective muscarinic M3 antagonists, are currently the preferred choice for management of COPD as they are more effective and have fewer side effects compared to β_2 -adrenoceptor agonists.

Bronchodilators improve symptoms but do not address the underlying chronic inflammation or the changes in airway structure (Hay D. W. P., Current Opinion in Chemical Biology (2000), 4, 412-419).

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Amongst phosphodiesterases, PDE 1V is the predominant sub-type in inflammatory cells, including mast cells, eosinophils, T lymphocytes, neutrophils and macrophages. It is also the dominant sub-type in structural cells such as sensory nerves and epithelial cells (Torphy T. J., Am. J. Resp. Crit. Care Med. (1998), 157, 351-370).

Standard treatment with corticosteroids as anti-inflammatory agents has demonstrated limited efficacy (Culpitt S. V., Maziak W., Loukidis S., Nightingale J. A., Matthews J. L., Barnes P. J., Am. J. Resp. Crit. Care Med. (1999), 160, 1635-9); Keatings V. M., Jatakanon A., Wordsell Y. M., Barnes P. J., Am. J. Resp. Crit. Care Med.

(1997), 155, 542-8). Selective PDE IV inhibitors, however, have proved to be very efficient in

attenuating the responses of various inflammatory cells through their ability to elevate cyclic AMP levels. They are known to modulate activity, migration and apoptosis of neutrophils by inhibiting the production and release of chemokines, superoxide free radicals, leukotrienes and proteolytic and toxic granular enzymes (Torphy T. J. , Am. J. Resp. Crit. Care Med. (1998), 157,351-370).

It has now been found that a combination of these two therapeutic activities, bronchodilatation with an Mg muscarinic antagonist and anti-inflammatory activity with a selective PDE IV inhibitor, in a single compound, provides a new and surprisingly effective approach to the treatment of COPD.

The compounds according to this invention are useful for treating respiratory disorders in connection with Chronic Obstructive Pulmonary Disease (COPD).

Preferred compounds have affinity for the human m3 muscarinic receptor at concentrations ranging from 100 nM to almost 1 nM and incorporate activity as selective phosphodiesterase IV (PDE IV) inhibitors at concentrations ranging from 2.5 μ M to almost 50 nM. These compounds also recognize the m1, m2, m4 and m5 receptors with variable receptor subtype selectivity.

Preferred compounds have been proven to antagonise carbachol-induced contraction of guinea-pig trachea in vitro.

In one aspect, the invention therefore provide compounds having the formula I, or a pharmaceutically acceptable salt thereof,

EMI2.1

wherein Y is -NH-R2 or a group of formula

<Desc/Clms Page number 3>

EMI3.1

R1 is cycloalkyl or non-substituted alkyl, R2 is cycloalkyl, R3 is hydrogen, alkyl, halogen, hydroxy, alkoxy or amino, or R2R3 is an alkylene bridging group, Ra is hydrogen, alkyl, alkenyl, alkynyl, halogen, hydroxy, alkoxy, amino, alkylamino, alkylsulfonyloxy, cyano, carboxy, ester or amido, Rb is hydrogen, alkyl or halogen, or RaRb is carbonyl, R4 is hydrogen or alkyl, R5 is cycloalkyl, arylalkyl or heterocycle-alkyl, or NR4R5 is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom, with the proviso that when Y is -NHR2 and R2R3 is an alkylene bridging group or when Y is a group of formula

EMI3.2

R1 is a cycloalkyl.

Compounds wherein Y is -NHR2 are named compounds Ia.

Compounds wherein Y represents a group of formula

EMI3.3

are named compounds Ib.

The term "alkyl", as used herein, is defined as including saturated, monovalent hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and 3-8 carbon atoms for cycloalkyl (in these two preferred cases, unless otherwise specified, "lower alkyl") and includes alkyl moieties substituted by 1 to 5 substituents independently selected from the group consisting of halogen, hydroxy, thiol, amino, nitro,

cyano, acyl derivative, sulfonyl derivative, sulfinyl derivative, alkylamino, carboxy, ester, ether, amido, azido, cycloalkyl, sulfonic acid, sulfonamide, thio derivative, esteroxy, amidooxy, heterocycle, vinyl, C1-6-alkoxy, C6-10-aryloxy, C6-10-aryl and oxo. "Non-substituted alkyl" represents saturated, monovalent

<Desc/Clms Page number 4>

hydrocarbon radicals having straight, branched or cyclic moieties or combinations thereof and containing 1-20 carbon atoms, preferably 1-6 carbon atoms for non-cyclic alkyl and

The term "halogen", as used herein, includes an atom of Cl, Br, F, I.

The term "hydroxy", as used herein, represents a group of the formula -OH.

The term "amino", as used herein, represents a group of the formula -NH₂.

The term "thiol", as used herein, represents a group of the formula -SH.

The term "cyano", as used herein, represents a group of the formula -CN.

The term "nitro", as used herein, represents a group of the formula -NO₂.

The term "alkoxy", as used herein, is defined as including -O-R₆ groups wherein R₆ represents an alkyl or a cycloalkyl group. Non-limiting examples are methoxy and ethoxy.

The term "arylalkyl", as used herein, represents a group of the formula -R₇-aryl in which R₇ is C 1-12- straight, branched or cyclic alkylene. Non-limiting examples are benzyl, halobenzyl, cyanobenzyl, methoxybenzyl, nitrobenzyl, 2-phenylethyl, diphenylmethyl, (4-methoxyphenyl) diphenylmethyl and anthracenylmethyl.

The term "aryl" as used herein, is defined as including an organic radical derived from an aromatic hydrocarbon consisting of 1-3 rings and containing 6-30 carbon atoms by removal of one hydrogen, such as phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, hydroxy, thiol, amino, nitro, cyano, C1-6-alkoxy, C1-6-alkylthio, C1-6-alkyl, C1-6-haloalkyl. Aryl radicals are preferably monocyclic containing 6-10 carbon atoms.

Preferred aryl groups are phenyl and naphthyl each optionally substituted by 1 to 5 substituents independently selected from halogen, nitro, amino, azido, C 1-6-alkoxy, C 1-6-alkylthio, C 1-6-alkyl and C 1-6-haloalkyl.

The term "alkylthio", as used herein, is defined as including -S-R_{6a} groups wherein R_{6a} represents an alkyl or a cycloalkyl group. Non-limiting examples are methylthio, ethylthio, propylthio and butylthio.

The term "heterocycle", as used herein is defined as including an aromatic or non aromatic cyclic alkyl, alkenyl, or alkynyl moiety as defined above, having at least one O, S and/or N atom interrupting the carbocyclic ring structure and optionally, one of the carbon of the carbocyclic ring structure may be replaced by a carbonyl. Non-limiting examples of aromatic heterocycles are pyridyl, furyl, pyrrolyl, thienyl, isothiazolyl, imidazolyl, benzimidazolyl, tetrazolyl, quinazolinyl, quinoliziny, naphthyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, quinolyl, isoquinolyl, isobenzofuranyl, benzothienyl, pyrazolyl, indolyl, indoliziny, purinyl, isoindolyl, carbazolyl, thiazolyl, 1,2, 4-thiadiazolyl, thieno (2,3-b) furanyl,

furopyranyl, benzofuranyl, benzoxepinyl, isooxazolyl, oxazolyl, thianthrenyl, benzothiazolyl, or benzoxazolyl, cinnolinyl, phthalazinyl, quinoxalinyl, phenanthridinyl, acridinyl, perimidinyl, phenanthrolinyl, phenothiazinyl, furazanyl, isochromanyl, indolinyl,

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xanthenyl, hypoxanthinyl, pteridinyl, 5-azacytidinyl, 5-azauracilyl, triazolopyridinyl, imidazolopyridinyl, pyrrolopyrimidinyl, and pyrazolopyrimidinyl optionally substituted by alkyl or as described above for the alkyl groups. Non-limiting examples of non aromatic heterocycles are tetrahydrofuranyl, tetrahydropyranyl, piperidinyl, piperidyl, piperazinyl,

salts, by treatment with appropriate organic and inorganic bases. Appropriate base salt forms include, for example, ammonium salts, alkali and earth alkaline metal salts, e. g. lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e. g. N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginin, lysine and the like.

Conversely said salt forms can be converted into the free forms by treatment with an appropriate base or acid.

Compounds of the formula I and their salts can be in the form of a solvate, which is included within the scope of the present invention. Such solvates include for example hydrates, alcoholates and the like.

Some of the compounds of formula I and some of their intermediates have at least one stereogenic center in their structure. This stereogenic center may be present in a R or a S configuration, said R and S notation is used in correspondance with the rules described in Pure Appl. Chem. , 45 (1976) 11-30.

The invention also relates to all stereoisomeric forms such as enantiomeric and diastereomeric forms of the compounds of formula I or mixtures thereof (including all possible mixtures of stereoisomers). Reference to a compound or compounds is intended to encompass that compound in each of its possible isomeric forms and mixtures thereof unless the particular isomeric form is referred to specifically.

Some of the compounds of formula I may also exist in tautomeric forms. Such forms although not explicitly, indicated in the above formula, are intended to be included within the scope of the present invention.

The invention also includes within its scope pro-drug forms of the compounds of formula I and its various sub-scopes and sub-groups.

The term "prodrug" as used herein includes compound forms which are rapidly transformed in vivo to the parent compound according to the invention, for example, by hydrolysis in blood. Prodrugs are compounds bearing groups which are removed by biotransformation prior to exhibiting their pharmacological action. Such groups include moieties which are readily cleaved in vivo from the compound bearing it, which compound after cleavage remains or becomes pharmacologically active.

Metabolically cleavable groups form a class of groups well known to practitioners of the art. They include, but are not limited to such groups as alkanoyl (i. e. acetyl, propionyl, butyryl, and the like), unsubstituted and substituted carbocyclic aroyl (such as benzoyl, substituted benzoyl and 1- and 2-naphthoyl), alkoxy carbonyl (such as ethoxy carbonyl), trialkylsilyl (such as trimethyl- and triethylsilyl), monoesters formed with dicarboxylic acids (such as succinyl), phosphate, sulfate, sulfonate,

<Desc/Clms Page number 8>

sulfonyl, sulfinyl and the like. The compounds bearing the metabolically cleavable groups have the advantage that they may exhibit improved bioavailability as a result of enhanced solubility and/or rate of absorption conferred upon the parent compound by virtue of the presence of the metabolically cleavable group. T. Higuchi and V. Stella, "Pro-drugs as Novel Delivery System", Vol. 14 of the A. C. S. Symposium Series; "Bioreversible Carriers in Drug Design", ed. Edward B. Roche, American Pharmaceutical Association and Pergamon Press, 1987.

According to a first embodiment of the invention compounds are compounds of formula Ia

EMI8.1

or a pharmaceutically acceptable salt thereof wherein R₁, R₂, R₃, R₄ and R₅ are as defined above.

Usually, R₁ is C₃-7-cycloalkyl or non-substituted alkyl.

Usually, R₂ is C₃-7-cycloalkyl, R₃ being as defined above, or R₂R₃ is a C₂-4 alkylene bridging group.

Usually, R₃ is hydrogen, C₁-4-alkyl, halogen, hydroxy, alkoxy or amino, R₂ being as defined above, or R₂R₃ is a C₂-4 alkylene bridging group.

Usually, R₄ is hydrogen or C₁-4-alkyl, R₅ being as defined above, or NR₄R₅ is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom.

Usually, R₅ is C₃-7-cycloalkyl, arylalkyl or heterocycle-alkyl, R₄ being as defined above, or NR₄R₅ is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom.

Generally R₁ is a non-substituted alkyl, a non-substituted cycloalkyl, a cycloalkyl substituted by a lower alkyl, or an alkyl substituted by a cycloalkyl.

Preferably, R₁ is C₃-4-alkyl or C₃-5-cycloalkyl, more preferably R₁ is selected from the group of cyclopropyl, isopropyl, cyclobutyl, cyclopentyl, 2-methyl-cyclopropyl and cyclopropylmethyl.

<Desc/Cims Page number 9>

Generally R₂ is a non-substituted cycloalkyl, or a cycloalkyl substituted by a lower alkyl or an aryl.

Preferably, R₂ is a non-substituted C₃-4-cycloalkyl. More preferably R₂ is selected from cyclopropyl or cyclobutyl.

Generally R₃ is hydrogen, halogen, amino, non-substituted alkoxy or a non-substituted alkyl.

Preferably, R₃ is hydrogen, methyl, ethyl, a Cl atom, a F atom, a Br atom, amino or methoxy.

In other preferred embodiments R₂R₃ is an alkylene bridging group selected from ethylene, propylene and butylene.

Generally R₄ is hydrogen or a non-substituted alkyl.

Preferably, R₄ is hydrogen or Cl-4-alkyl. More preferably R₄ is hydrogen or methyl.

Preferably, R₅ is 2- (2-thienyl) ethyl, 2-furylmethyl, 2-thienylmethyl, 4- pyridinylmethyl, benzyl, 2- (methylsulfanyl) benzyl, 2, 6-difluorobenzyl, 2-fluorobenzyl, 2-nitrobenzyl, 3,5-bis (trifluoromethyl) benzyl, 3, 5-difluorobenzyl, cyclohexyl, cycloheptyl, 4-methylcyclohexyl, or 2, 2-diphenylethyl.

In other preferred embodiments, NR₄R₅ is 1, 3-thiazolidin-3-yl, 1-azepanyl, 1- azocanyl, 3, 5-dimethyl-1-piperidinyl, 4- (2-methoxyphenyl)-1-piperidinyl, 4- (hydroxy (diphenyl)methyl)-1-piperidinyl, 4- (trifluoromethyl)-1-piperidinyl, 4,4-difluoro-1-piperidinyl, 4, 4-dimethyl-1-piperidinyl, 4-carbamoyl-1-piperidinyl, 4-benzyl- 1-piperidinyl, 4-carboxy-1-piperidinyl, 4-cyano-4-phenyl-1-piperidinyl, 4-ethoxycarbonyl-1-piperidinyl, 4-ethyl-1-piperidinyl, 4-ethyl-4-methyl-1-piperidinyl, 4-hydroxy-1-piperidinyl, 4-hydroxy-4-phenyl-1-piperidinyl, 4-hydroxymethyl-1- piperidinyl, 4-methyl-1-piperidinyl, 4-methylene-1-piperidinyl, 4-oxo-1-piperidinyl, 3,6-dihydro-1 (2H)-pyridinyl, 3-azabicyclo [3.2.1] oct-3-yl, 4-thiomorpholinyl, 2-one-1- azepanyl, 3,4-dihydro-2(1H)-isoquinolinyl, 1,4-dioxo-8-azaspiro [4.5] dec-8-yl, 1,3, 3- trimethyl-6-azabicyclo [3.2.1] oct-6-yl, octahydro-2(1H)-isoquinolinyl or 8- azaspiro [4.5] dec-8-yl.

Combinations of one or more of these preferred compound groups are especially preferred.

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More preferred compounds Ia are: 6- (1-azepanyl)-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine ; 6- (1- azepanyl) -N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; 6-(1-azepanyl)-5-chloro-N, 2-dicyclopropyl-4-pyrimidinamine ; 6- (1-azepanyl)-N, 2-dicyclopropyl-5-fluoro-4-pyrimidinamine ; 6-azepan-1-yl-5-bromo-N,2-dicyclopropyl-4-pyrimidinamine ; 6- (1- azepanyl) -N, 2-dicyclopropyl-4-pyrimidinamine ; 6- (1-azepanyl)-N₄, 2-dicyclopropyl-4, 5- pyrimidinediamine ; 6- (1-azepanyl)-N-cyclopropyl-2-isopropyl-5-methyl-4- pyrimidinamine ; 6- (1-azepanyl)-N-cyclopropyl-5-methyl-2- (2-methylcyclopropyl)-4- pyrimidinamine ; 6- (1-azocanyl)-N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; N, 2- dicyclopropyl-5-methyl-6- [4- (trifluoromethyl)piperidin-1-yl]-4-pyrimidinamine ; N, 2-dicyclopropyl-6- (4, 4-difluoro-1-piperidinyl)-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-6- (4, 4-dimethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-6- (4-ethyl-1-piperidinyl)-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-5-ethyl-6- (4-methyl-1-piperidinyl)-4-pyrimidinamine ; N,2-dicyclopropyl-5-methyl-6- (4- methyl-1-piperidinyl)-4-pyrimidinamine ; N-cyclopropyl-5-methyl-2- (2-methylcyclopropyl)-6- (4-methyl-1-piperidinyl)-4-pyrimidinamine ; N, 2-dicyclopropyl-5-methyl-6- (4-methylene-1-piperidinyl)-4-pyrimidinamine ; N,2-dicyclopropyl-6- (3, 6- dihydro-1(2H)-pyridinyl)-5-methyl-4-pyrimidinamine ; 6- (3-azabicyclo [3.2. 1] oct-3-yl)- N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; N,2-dicyclopropyl-5-ethyl-6- (4-thiomorpholinyl)-4-pyrimidinamine ; N,2-dicyclopropyl-5-methyl-6- (4-thiomorpholinyl)- 4-pyrimidinamine ; N₄,2-dicyclopropyl-N₆-(2, 6-difluorobenzyl) -5-methyl-4,6- pyrimidinediamine ; N₄-cyclohexyl-N₆-cyclopropyl-2-(2-methylcyclopropyl)-4, 6- pyrimidinediamine ; N₄, 2-dicyclopropyl-5-methyl-N₆-(4-methylcyclohexyl)-4, 6- pyrimidinediamine ; 6- (1-azepanyl)-2-cyclopentyl-N-cyclopropyl-5-methyl-4- pyrimidinamine ; 4-azepan-1-yl-2-cyclopropyl-5, 6,7, 8-tetrahydro-pyrido [2,3-d]pyrimidine ; 4-azepan-1-yl-2-cyclopropyl-6,7, 8, 9-tetrahydro-pyrimido [4,5-b] azepine ; N, 2-dicyclopropyl-5-methyl-6-(1-piperidinyl)-4-pyrimidinamine ; 6- (3- azabicyclo [3.2. 2] non-3-yl)-N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-5-methyl-6-(2-methyl-1-piperidinyl)-4-pyrimidinamine and N, 2- dicyclopropyl-5-methyl-6- (1-pyrrolidinyl)-4-pyrimidinamine, stereoisomeric forms or mixtures thereof, or pharmaceutically acceptable salts thereof.

Most preferred compounds Ia are:

6-(1-azepanyl)-N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-6- (4, 4-dimethyl-1-piperidiny)-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-5-methyl-6- (4-methyl-1-piperidiny)-4-pyrimidinamine ; 6- (3- azabicyclo [3.2. 1]oct-3-yl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine ; N, 2-dicyclopropyl-5-methyl-6- (4-thiomorpholinyl)-4-pyrimidinamine ; 4-azepan-1-yl-2-

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cyclopropyl-5,6, 7,8-tetrahydro-pyrido [2, 3-d] pyrimidine and 4-azepan-1-yl-2cyclopropyl-6,7, 8,9-tetrahydro-pyrimido [4,5-b] azepine, or pharmaceutically acceptable salts thereof.

According to another embodiment of the invention, compounds are compoundsIb, or a pharmaceutically acceptable salt thereof,

EMI11.1

wherein Y is a group of formula

EMI11.2

andR1, R3,Ra, Rb,R4 and R5 are as defined above.

Usually, R1 is C3-7-cycloalkyl.

Usually,R3 is hydrogen,Cl-4-alkyl, halogen, hydroxy, alkoxy or amino.

Usually, Ra is hydrogen,C1-4-alkyl, C2-6-alkenyl, C2-6-alkynyl, halogen, hydroxy, alkoxy, amino, alkylamino, alkylsulfonyloxy, cyano, carboxy, ester or amido,Rb being as defined above, or RaRb is carbonyl.

Usually,Rb is hydrogen,C 1-4-alkyl or halogen, Ra being as defined above, or RaRb is carbonyl.

Usually, NR4R5 is a heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom.

Generally, R1 is a non-substituted C3-7-cycloalkyl, or a C3-7-cycloalkyl substituted by a lower alkyl.

Preferably, R1 is C3-4-cycloalkyl. More preferably, R1 is cyclopropyl.

Generally R3 is hydrogen, halogen, amino, non-substituted alkoxy or a non- substitutedCl-4-alkyl.

Preferably,R3 is hydrogen orCl-4-alkyl. More preferably,R3 is hydrogen or methyl.

Generally, Ra is hydrogen,C 1-4-alkyl, halogen, hydroxy, alkoxy, alkylsulfonyloxy or cyano.

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Preferably, Ra is hydrogen, methyl, hydroxy, methoxy, methylsulfonyloxy, a Br atom, a F atom or cyano. More preferably, Ra is hydrogen, methyl, hydroxy or a F atom.

Generally,Rb is hydrogen orC 1-4-alkyl.

Preferably,Rb is hydrogen or methyl. More preferably,Rb is hydrogen.

In other preferred embodiments RaRb is carbonyl.

Preferably, NR4R5 is a 5-to 9-membered heterocycle, which may be substituted, containing only one heteroatom which is a nitrogen atom or containing two heteroatoms wherein one is a nitrogen atom and the other is a non-oxidized sulfur atom. More preferably, NR4R5 is 1-azepanyl.

Combinations of one or more of these preferred compound groups are especially preferred.

More preferred compounds Ib are: 1- (6-azetidin-1-yl-2-cyclopropyl-5-methylpyrimidin-4-yl) azepane; 1- [2-cyclopropyl-5-methyl-6- (3-methylazetidin-1-yl) pyrimidin-4-yl] azepane ; 1-(6-azepan-1-yl-2-cyclopropyl-5-methylpyrimidin-4-yl) azetidin-3-ol ; 1- [2-cyclopropyl-6- (3- methylazetidin-1-yl) pyrimidin-4-yl] azepane; 1- (6-azetidin-1-yl-2-cyclopropylpyrimidin- 4-yl) azepane and 1- [2-cyclopropyl-6- (3-fluoroazetidin-1-yl)-5-methylpyrimidin-4-yl] azepane, or pharmaceutically acceptable salts thereof.

Most preferred compounds Ib are: 1- (6-azetidin-1-yl-2-cyclopropyl-5-methylpyrimidin-4-yl) azepane and 1- [2-cyclopropyl-5-methyl-6- (3-methylazetidin-1-yl) pyrimidin-4-yl] azepane, or pharmaceutically acceptable salts thereof.

The present invention concerns also processes for preparing the compounds of formula I.

The following process description sets forth certain synthesis processes in an illustrative manner. Other alternative and/or analogous methods will be readily apparent to those skilled in this art.

A. According to one embodiment, compounds having the general formula I wherein R3 = H, alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a

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compound of formula II wherein R3 = H, alkyl, halogen, alkoxy or hydroxy with an amine of formula III according to the equation:

EMI13.1

This reaction may be carried out without solvent in the case of high-boiling point amines of formula III or in a high-boiling point alcohol (e. g.: 1-methoxy-2propanol) as solvent in the case of solid or low boiling point amines of formula III, between 80 and 130 C.

Compounds of formula III are commercially available or may be prepared under any conventional methods known to the person skilled in the art.

Compounds of formula II

EMI13.2

wherein R3 = H, alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula IV wherein R3 = H, alkyl, halogen, alkoxy or hydroxy either with a primary amine of formula Va (leading to compounds IIa), or with an azetidine of formula Vb (leading to compounds IIb) according to the equations:

EMI13.3

These reactions may be carried out without solvent or in dichloromethane as a solvent, between 30 and 60 C, in the presence of a base such as potassium carbonate in the case of an azetidine hydrochloride.

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Compounds of formula Va are commercially available and compounds of formula Vb are either commercially available or may be prepared under any conventional method known to the person skilled in the art.

As an example, 3-fluoroazetidine hydrochloride may be prepared by catalytic hydrogenation of 1-benzhydryl-3-fluoroazetidine. This reaction can be performed by any person skilled in the art. 1-benzhydryl-3-fluoroazetidine may be prepared by fluorination of 1-benzhydryl-3-methanesulfonyloxyazetidine. This reaction may be carried out in boiling acetonitrile in the presence of tetrabutylammonium fluoride as a fluorinating agent as described in: Berkin A., Szarek W. A., Kisilevsky R., Carbohydr. Res. (2000), 326,250- 263.

Compounds of formula IV wherein R3 = H, alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula VI wherein R3 = H, alkyl, halogen, alkoxy or hydroxy with phosphorus oxychloride according to the equation:
EMI14.1

This reaction may be carried out in boiling phosphorus oxychloride in the presence of one equivalent of N, N-diethylaniline as described in: Evans R. F., Savage G. P., Gough D. A., Aust. J. Chem. (1990), 43,733-740 or in: Biagi G., Giorgil., Livi O., Scartoni V., Lucacchini A., Farmaco (1997), 52,61-66.

Compounds of formula VI wherein R3 = H, alkyl, halogen, alkoxy or hydroxy may be prepared by reaction of a compound of formula VII with a dialkylmalonate of formula VIII wherein R3 = H, alkyl, halogen, alkoxy or hydroxy and R8 = C 1-4-alkyl according to the equation:
EMI14.2

This reaction may be carried out in an alcoholic solvent, for example methanol or ethanol, in the presence of 2 equivalents of metallic sodium as a base between 60 and 80 C as described in: Gershon H., Braun R., Scala A., Rodin R., J. Med. Chem.

(1964), 7,808.

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Compounds of formula VIII are commercially available or may be prepared under any conventional method known to the person skilled in the art.

Compounds of formula VII are commercially available or may be prepared from the corresponding nitrile IX according to the equation:
EMI15.1

This reaction may be carried out as described in: Moss R. A., Liu W., Krogh-Jespersen K., Tetrahedron Lett. (1993), 34,6025-6028.

B. According to another embodiment, compounds having the general formula I wherein $R_3 = NH_2$ may be prepared by reduction of the corresponding compound of formula I-A according to the equation:
EMI15.2

This reaction may be carried out by any conventional method known to the person skilled in the art, for example aqueous sodium dithionite in dioxane in the presence of ammonia as described in: Chorvat R. J. et al. , J. Med. Chem. (1999), 42, 833-848.

Compounds of formula I-A wherein $R_3 = NO_2$ may be prepared from a compound VI wherein $R_3 = NO_2$ following the procedure described in A, using compound of formula
EMI15.3
as an intermediate.

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Compounds of formula VI wherein $R_3 = NO_2$ may be prepared by reaction of the corresponding compound of formula VI wherein $R_3 = H$ with nitric acid according to the equation:

EMI16.1

(VI) with $R_3 = H$ (VI) with $R_3 = NO_2$

This reaction may be carried out using fuming nitric acid in glacial acetic acid between 30 and 40 C as described in: Beck J. P. et al. , Bioorg. Med. Chem. Lett.

(1999), 9,967 or in: Bagli J. et al. , J. Med. Chem. (1988), 31,814.

C. According to another embodiment, compounds having the general formula I wherein $R_3 = Br$ may be prepared by bromination using N-bromosuccinimide (NBS) of a compound of formula I wherein $R_3 = H$ according to the equation:

EMI16.2

This reaction may be carried out in chloroform as described in: Chen C., Dagnino R. , De Souza E. B., Grigoriadis, D. E. , Huang C.Q., J. Med. Chem. (1996) 39,4358-4360.

D. According to another embodiment, compounds having the general formula Ia wherein R_2R_3 is an alkylene bridging group of formula $-(CH_2)_n-CH_2-$, with $n = 1-6$ may be prepared by reaction of a compound of formula X wherein $n = 1-6$ with an amine of formula III according to the equation:

EMI16.3

This reaction may be carried out without solvent in the case of high-boiling point amines of formula III or in a high-boiling point alcohol (e. g.: 1-methoxy-2propanol) as solvent in the case of solid or low boiling point amines of formula III, between 80 and 130 C.

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D.1 Compounds of formula X wherein $n = 2-6$ may be prepared by heating a compound of formula IV wherein R_3 represents $-(CH_2)_n-NH_2$ with $n = 2-6$ according to the equation:

EMI17.1

(IV) with $R_3 = -(CH_2)_n-NH_2$ (X) This reaction may be carried out in a high-boiling point alcohol

(e. g.:1-methoxy-2-propanol) as solvent, between 120 and 140 C.

Compounds of formula IV wherein R₃ represents -CH₂-(CH₂)_n-NH₂, with n = 2-6, may be prepared by reaction of a compound of formula VI wherein R₃ represents CH₂-(CH₂)_n-NHBoc, with n = 2-6, with phosphorus oxychloride according to the equation:

EMI17.2

(VI) with R₃ = -CH₂-(CH₂)_n-NH₂ (IV) with R₃ = -CH₂-(CH₂)_n-NH₂ This reaction may be carried out in boiling phosphorus oxychloride in the presence of 1 equivalent of N, N-diethylaniline as described in Evans R. F., Savage G. P., Gough D. A., Aust. J. Chem. (1990), 43,733-740 or in: Biagi G., Giorgi I., Livi O., Lucacchini A., Farmaco (1997), 52,61-66.

Compounds of formula VI wherein R₃ represents -CH₂-(CH₂)_n-NHBoc, with n = 2-6, may be prepared by reaction of a compound of formula VII with a dialkylmalonate of formula VIII wherein R₃ represents -CH₂-(CH₂)_n-NHBoc, with n = 2-6, according to the procedure described in A.

Compounds of formula VIII wherein R₃ represents -CH₂-(CH₂)_n-NHBoc, with n = 2-6, may be prepared by reaction the corresponding compound of formula VIII wherein R₃ = H and R₈ = Cl-4-alkyl with a compound of formula XI wherein L is a leaving group according to the equation:

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EMI18.1

This reaction may be carried out starting from protected alkyl amines bearing a leaving group L (e. g.: halogen, mesylate) in an alcoholic solvent, for example methanol or ethanol, in the presence of 2 equivalents of metallic sodium as a base between 60 and 80 C.

Compounds of formula VIII are commercially available.

Compounds of formula XI may be prepared by any conventional methods known to the person skilled in the art.

D. 2 Compounds of formula X wherein n = 1 may be prepared by reaction of a compound of formula XII with phosphorus oxychloride according to the equation:

EMI18.2

This reaction may be carried out in boiling phosphorus oxychloride.

Compounds of formula XII may be prepared by reaction of a compound of formula VII with 2-ethoxy-4, 5-dihydro-3H-pyrrole-3-carboxylic acid ethyl ester (XIII) according to the equation:

EMI18.3

This reaction may be carried out in an alcoholic solvent, for example methanol or ethanol, in the presence of 1 equivalent of metallic sodium as a base between 60 and 80 C as described in: Gershon H., Braun R., Scala A., Rodin R., J. Med. Chem. (1964), 7,808 and in: Granik V. G., Glushkov R. G., Pharm.

Chem. J. (Engl. Transl.) (1967), 5,247-249.

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2-Ethoxy-4,5-dihydro-3H-pyrrole-3-carboxylic acid ethyl ester of formula (XIII) may be prepared as described in: Granik V. G. , Glushkov R. G. , Pharm. Chem.

J. (Engl. Transl.) (1967), 5,247-249 and in: Lindstrom K. J. , Crooks S. L., Synth. Commun. (1990), 2335-2337.

E. According to another embodiment, compounds having the general formula Ib wherein Ra = Br may be prepared by bromination using sodium bromide of a compound of formula Ib wherein Ra =OSO₂CH₃ according to the equation:

EMI19.1

This reaction may be carried out in N, N-dimethylformamide between 80 and 120 C as described in: Okada T., Ezumi K. , Yamakawa M. , Sato H., Tsuji T., Chem Pharm. Bull. (1993), 41,126-131.

Compounds having the general formula Ib wherein Ra =OSO₂CH₃ may be prepared by mesylation using methanesulfonyl chloride of a compound of formula Ib wherein Ra = OH. This reaction may be carried out by any person skilled in the art.

F. According to another embodiment, compounds having the general formula Ib wherein Ra = CN may be prepared by cyanation using sodium cyanide of a compound of formula Ib wherein Ra =OSO₂CH₃ according to the equation:

EMI19.2

This reaction may be carried out in N, N-dimethylformamide between 80 and 120 C as described in: Frigola J., Pares J. , Corbera J. , Vano D. , Merce R. , J. Med.

Chem. (1993), 36,801-810.

G. According to another embodiment, compounds having the general formula Ib wherein RaRb = carbonyl may be prepared by oxidation using sulfur

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trioxide/pyridine complex of a compound of formula Ib wherein Ra = OH according to the equation: EMI20.1

This reaction may be carried out in dimethylsulfoxide at room temperature as described in: Katritzky A. R. , Cundy D. J. , Chen J. , J. Heterocyclic Chem. (1994), 31, 271-276.

When compounds of formula I present one or several stereogenic centres, and that non-stereoselective methods of synthesis are used, resolution of the mixture of stereoisomers can best be effected in one or several steps, involving generally sequential separation of mixtures of diastereomers into their constituting racemates, using preferably chromatographic separations on achiral or chiral phase in reversed or preferably in direct mode, followed by at least one ultimate step of resolution of each racemate into its enantiomers, using most preferably chromatographic separation on chiral phase in reversed or preferably in direct mode. Alternatively, when partly stereoselective methods of synthesis are used, the ultimate step may be a separation of diastereomers using preferably chromatographic separations on achiral or chiral phase in reversed or preferably in direct mode.

In another embodiment, the present invention concerns also the synthesis intermediates of formula II

EMI20.2

wherein Y, R1 and R2 are as defined above, R3 is hydrogen, alkyl, halogen, alkoxy or hydroxy, Ra is hydrogen, alkyl, alkenyl, alkynyl, halogen, hydroxy, alkoxy, amino, alkylamino, alkylsulfonyloxy, cyano, carboxy, ester or amido, and Rb is hydrogen, alkyl or halogen or RaRb is carbonyl.

In synthesis intermediates of formula II, when Y represents a group of formula :

EMI20.3

<Desc/Clms Page number 21>

then R1 is preferably cycloalkyl, more preferably cyclopropyl and R3 is preferably hydrogen or alkyl, more preferably hydrogen or methyl.

In a preferred embodiment, the present invention also concerns the synthesis intermediates selected from the group consisting of 6-chloro-N, 2-dicyclopropyl-5-fluoro-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine ; 5,6-dichloro-N, 2-dicyclopropyl-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-methoxy-4-pyrimidinamine ; 6-chloro-N, 2-dicyclopropyl-5-ethyl-4-pyrimidinamine ; N- [6-chloro-2- (2-trans-methylcyclopropyl)-4-pyrimidinyl]-N-cyclopropylamine and its enantiomers; 6-chloro-N-cyclopropyl-5-methyl-2-(2-trans-methylcyclopropyl)-4-pyrimidinamine ; 6-chloro-N-cyclopropyl-5-methyl-2-(2-cis-methylcyclopropyl)-4-pyrimidinamine ; N- [6-chloro-2-(cyclopropylmethyl)-5-methyl-4-pyrimidinyl]-N-cyclopropylamine ; 6-chloro-2-cyclobutyl-N-cyclopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-N-cyclobutyl-2-cyclopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-N-cyclopropyl-2-isopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-2-cyclopentyl-N-cyclopropyl-5-methyl-4-pyrimidinamine ; 6-chloro-2-cyclopropyl-5-methyl-N- (2-methylcyclopropyl)-4-pyrimidinamine ; 6-chloro-2-cyclopropyl-5-methyl-N- (2-phenylcyclopropyl)-4-pyrimidinamine ; 4- (1-azetidiny)-6-chloro-2-cyclopropyl-5-methylpyrimidine; 4- (1-azetidiny)-6-chloro-2-cyclopropylpyrimidine ; 4-chloro-2-cyclopropyl-5-methyl-6- (3-methyl-1-azetidiny) pyrimidine ; 4-chloro-2-cyclopropyl-6- (3-methyl-1-azetidiny) pyrimidine ; 4-chloro-2-cyclopropyl-6- (3, 3-dimethyl-1-azetidiny)-5-methylpyrimidine ; 1- (6-chloro-2-cyclopropyl-5-methyl-4-pyrimidinyl)-3-azetidinol ; 4-chloro-2-cyclopropyl-6-(3-fluoro-1-azetidiny)-5-methylpyrimidine ; 4-chloro-2-cyclopropyl-6- (3-fluoro-1-azetidiny) pyrimidine and 4-chloro-2-cyclopropyl-6-(3-methoxy-1-azetidiny)-5-methylpyrimidine.

In another embodiment, the present invention concerns the following synthesis intermediate of formula II-A : 6-chloro-N, 2-dicyclopropyl-5-nitro-4-pyrimidinamine.

In another embodiment, the present invention concerns the following synthesis intermediate of formula VII: 2-methylcyclopropanecarboximidamide.

In another embodiment, the present invention concerns the synthesis intermediates of formula VI

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EMI22.1

wherein R1 is alkyl or cycloalkyl and R3 is alkoxy. Usually, R1 is alkyl or C3-5- cycloalkyl.

In a preferred embodiment, the present invention also concerns the synthesis intermediates selected from the group consisting of : 2-cyclopropyl-5-fluoro-4,6- pyrimidinediol ; 5-chloro-2-cyclopropyl-4, 6-

pyrimidinediol ; 2-cyclopropyl-5-methoxy- 4,6-pyrimidinediol ; 2-cyclopropyl-5-ethyl-4,6-pyrimidinediol ; 2- (2-methylcyclopropyl)- 4,6-pyrimidinediol ; 5-methyl-2-(2-methylcyclopropyl)-4, 6-pyrimidinediol ; 2-(cyclopropylmethyl) -5-methyl-4, 6-pyrimidinediol ; 2-cyclobutyl-5-methyl-4,6-pyrimidinediol ; 2-isopropyl-5-methyl-4, 6-pyrimidinediol ; 2-cyclopentyl-5-methyl-4, 6-pyrimidinediol ; [3-(2-cyclopropyl-4, 6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester and [4-(2-cyclopropyl-4, 6-dihydroxy-pyrimidin-5-yl)-butyl]-carbamic acid tert-butyl ester.

In another embodiment, the present invention concerns the following synthesis intermediates of formula IV : 4, 6-dichloro-2-cyclopropyl-5-fluoropyrimidine ; 4,5, 6- trichloro-2-cyclopropylpyrimidine ; 4,6-dichloro-2-cyclopropyl-5-pyrimidinyl methyl ether; 4, 6-dichloro-2-cyclopropyl-5-ethylpyrimidine ; 4,6-dichloro-2- (2- methylcyclopropyl) pyrimidine; 4,6-dichloro-5-methyl-2- (2- methylcyclopropyl) pyrimidine ; 4,6-dichloro-2- (cyclopropylmethyl)-5-methylpyrimidine ; 4, 6-dichloro-2-cyclobutyl-5-methylpyrimidine ; 4,6-dichloro-2-isopropyl-5- methylpyrimidine and 4, 6-dichloro-2-cyclopentyl-5-methylpyrimidine.

In another embodiment, the present invention concerns the following synthesis intermediate of formula I-A : 6- (1-azepanyl)-N, 2-dicyclopropyl-5-nitro-4- pyrimidinamine.

In another embodiment, the present invention concerns the synthesis intermediates of formula X
EMI22.2
wherein n is 1-6 and R1 is cycloalkyl.

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Preferably, the synthesis intermediates of formula X are selected from the group consisting of : 4-chloro-2-cyclopropyl-6, 7-dihydro-5H-pyrrolo [2, 3-d] pyrimidine ; 4-chloro-2-cyclopropyl-5,6, 7, 8-tetrahydro-5H-pyrido [2,3-d] pyrimidine and 4-chloro-2- cyclopropyl-6, 7,8,9-tetrahydro-5H-pyrimido [4,5-b] azepine.

In another embodiment, the present invention concerns the synthesis intermediates of formula XII
EMI23.1
wherein R1 is cycloalkyl.

Preferably, the synthesis intermediate of formula XII is 2-cyclopropyl-6,7- dihydro-5H-pyrrolo [2,3-d] pyrimidin-4-ol.

It has now been found that compounds of formula I and their pharmaceutically acceptable salts are useful in a variety of pharmaceutical indications.

For example, the compounds according to the invention are useful for the treatment of respiratory disorders in connection with the Chronic Obstructive Pulmonary Disease (COPD).

These compounds may also be used for treating symptoms related to disorders such as chronic bronchitis, emphysema, cough, either directly linked to COPD or not, and also cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis and asthma.

Preferred compounds have antagonist activity against the human m3 muscarinic receptor at concentrations ranging from 100 nM to almost 1 nM and incorporate activity as selective phosphodiesterase IV (PDEIV) inhibitors at concentrations ranging from 2.5yM to almost 50 nM. These

compounds also recognize the m1, m2, m4 and m5 receptors with variable receptor subtype selectivity.

Preferred compounds have been proven to antagonise carbachol-induced contraction of guinea-pig trachea in vitro.

In addition the compounds according to the invention may be used in the treatment of the following symptoms which are related to PDE IV or M3 : PDE IV-related

Amongst PDEs, PDE IV is highly selective for cAMP. Four human PDE IV subtypes have been identified, with distinct tissue and cellular distribution. PDEIVA

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appears to be distributed ubiquitously. PDE IVB is expressed in heart, brain, skeletal muscle and lung. PDE IVC is abundant in neuronal tissue but is absent from immune and inflammatory cells. PDE IVD is abundant in immune and inflammatory cells.

Functional effects such as those associated with gastric acid secretion, relaxation of the myometrium, bronchorelaxation and diuresis in the kidney have been attributed to the effect of PDE IV inhibition. This argues in favour of the interest of such approach for treating GI disorders, kidney dysfunction, respiratory and inflammatory disorders.

Furthermore, PDE IV may also be of biological significance and therapeutic relevance in CNS therapeutic indications such as depression and dementia. The hypothesis is that enhanced cAMP availability produced by inhibition of PDE IV stimulates the increase in noradrenaline function produced by classical antidepressants such as imipramine at the post-synaptic level (Achtel H. , Pharmacopsychiatry (1990), 23,27-32). Denbufylline has also been shown to increase cAMP in cortical slices, indicating a potential in the treatment of cognitive impairment (Nicholson C. D. , Psychopharmacology (1990), 101,147-159).

In addition, the PDE IV enzyme may also be a potential target for anticancer therapy, due to its inhibitory effect on tumour cell growth (Drees M., Zimmermann R., Eisenbrand G. , Cancer Res. (1993), 53,3058-3061), and PDE IV inhibition may be beneficial in tissue transplantation (Pinsky D. , Oz M., Morris S. , J. Clin. Invest. (1993), 92,2994-3002) and for cardiovascular diseases including atherosclerosis and hypertension (Demouliou-Mason C. , Exp. Opin. Ther. Patents (1994), 4, 813-823).

M3-related

Lower urinary tract disorders:

The parasympathetic nervous system is the principal excitatory innervation to the detrusor smooth muscle of the urinary bladder. Acetylcholine, released from postganglionic cholinergic nerves, activates postjunctional muscarinic receptors in the detrusor which causes contraction of the bladder that is coordinated with outlet relaxation and leads to voiding of urine (De Groat W. C. , Booth A. M. , Yoshimura N. , In: "Nervous control of the urogenital system", Maggi, C. A. (Ed), Harwood Academic Publishers, Amsterdam, (1993), 227-290). Both m2 and m3 muscarinic receptors are expressed in the smooth muscle of the bladder detrusor (Hegde S. S. , Eglon R. M., Life Science (1999), 64,419-428). Muscarinic m3 receptors play a key role in mediating the contractile effect of Acetylcholine (ACh) but m2 receptors may also contribute to micturition through opposing the relaxing effect of adrenergic sympathetic tone.

Prejunctional m1 facilitory muscarinic receptors may also be involved.

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Aging, inflammation or irritants and neurological trauma may result in increased nerve afferent and efferent activity and overactive bladder to become a leading cause of trouble presenting some symptoms such as urgency and frequency micturation and incontinence.

Therefore, non-selective muscarinic Mg antagonists have utility in the treatment of bladder disorders including urge and mixed urinary incontinence, pollakiuria, neurogenic or unstable bladder, hyperreflexia and chronic cystitis (Gillberg P.G., Sundquist S., Nilvebrant L., Eur. J. Pharmacol. (1998), 349, 285-292; Schwantes U., Topfmeler P., International Journal of Clinical Pharmacology and Therapeutics (1999), 37, 209-218; Andersson K. E. et al., In: "Incontinence. 1st International Consultation on Incontinence-June 28-July 1, 1998-Monaco", Abrams P., Khouri S., Wein A., Les Editions Vingt et Un, Paris, (1999), 447-486).

Gastrointestinal disorders:

Contractility of the smooth muscle of the gastrointestinal tract is under the control of parasympathetic tone and Acetylcholine (ACh). Contraction of the intestinal smooth muscle is principally dependent upon activation of muscarinic m3 receptors although stimulation of m2 muscarinic receptors might synergize with m3-mediated responses (Sawyer G. W., Ehlert F. J., J. Pharmacol. Exp. Ther. (1998), 284, 269-277).

Gastric secretion is also under the control of the parasympathetic nervous system. Secretagogue effect of ACh depend on the activation of post-junctional m3 receptors whilst m1 receptors located on the post-ganglionic nerves of the myenteric plexus have a facilitatory role on the parasympathetic nerve activity.

Therefore, m3 and m1 muscarinic receptor antagonists are potentially useful for treating gastrointestinal disorders associated with intestinal hypermotility such as irritable bowel syndrome, spastic colitis and diverticulosis (Wallis R. M., Napier C. M., Life Science (1999), 64, 395-401) and to reduce acid secretion, gastric motility, to aid the healing of peptic ulcers and to treat gastroesophageal reflux disease and stress-related erosive syndrome (Rademaker J. W., Hunt R. H., Scand. J. Gastroenterol.

(1990), 25, 19-26; Coruzzi G., Adami M., Bertaccini G., Arch. Int. Pharmacodyn. Ther.

(1989), 302, 232-241).

CNS-Cognitive disorders

The release of acetylcholine from central cholinergic nerves is under autoinhibitory control via m2 or m4 autoreceptors.

Therefore, M2 or M4 antagonists might reduce the levels of ACh released and may offer a potential approach for the treatment of cognitive disorders causally related to a deterioration or deficit of cortical cholinergic neurons, such as in senile dementia

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and Alzheimer's disease (Doods H. N., Quirion R., Mihm G., Life Science (1993), 52, 497-503).

CNS-Locomotor disorders

The nigrostriatum has many more m4 receptors than any other tissue (Santiago M. P., Potter L. T., Brain Res. (2001), 894, 12-20). These receptors exert inhibitory control on Dopamine (D1) receptor

mediated locomotor stimulation (Gomez J. , Zhang L. , Kostenis E. , Felder C. , Bymaster F. , Brodtkin J. , Shannon H. , Xia B. , Deng C. , Wess J. , Proc. Natl. Acad. Sci. USA. (1999), 96,10483-10488).

Therefore, centrally active M4 muscarinic antagonists may have the potential to treat Parkinsonian's disorders and dyskinesia thought to be causally related to a deterioration of dopaminergic neurons in the nigrostriatum (Salamone J. D. , Carlson B. B. , Correa M. , Wisniecki A. , Nisenbaum E. , Nisenbaum L. , Felder C. , In: "Society for Neuroscience 30th Annual Meeting New Orleans, Nov 2000", Mayorga et al. , (1999), Abstract 278. 5; Mayorga A. J. , Cousins M. S. , Trevitt J. T. , Conlan A. , Gianutsos G. , Salamone J. D. , Eur. J. Pharmacol. (1999), 364,7-11).

CNS-feeding disorders

Activation of muscarinic m3 receptors located in the lateral hypothalamus contributes to feeding behaviour (Yamada M. et al., Nature (2001), 410,207-212).

Thereby, M3 antagonists may offer new therapeutic perspectives for the treatment of obesity, bulimia and metabolic syndrome.

CNS-sleeping disorders

Activation of m1 and m3 receptors in the mediodorsal pontine tegmentum results in a marked increase in paradoxical sleep indicating that centrally active M4 antagonists can be useful for treating sleep disorders (Imeri L. , Bianchi S. , Angeli P. , Mancini M. , Brain Res. (1994), 636,68-72 ; Sakai, K. , Onoe H. , Eur. J. Neurosci.

(1997), 9,415-23).

Cardiovascular disorders

The heart rate is under parasympathetic tone via muscarinic m2 receptors on the SA node.

Therefore, m2 receptor antagonists are of potential value in the emergency treatment of acute myocardial infarction where the dominant autonomic influence of the heart is via the vagus nerve, causing sinus or nodal bradycardia (Van Zwieten P. A. , Doods H. N. , Cardiovascular Drugs and Therapy (1995), 9,159-167).

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Thus the present invention concerns a compound of formula I or a pharmaceutically acceptable salt thereof for use as a medicament.

In a further aspect, the present invention concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of PDE IV and/or M4 related disorders such as mentioned above.

In particular, the present invention concerns the use of a compound of formula I or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of COPD or of symptoms related to disorders such as chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress syndrome, rhinitis and asthma.

The present invention also concerns a method for treating COPD or symptoms related to disorders such as chronic bronchitis, emphysema, cough, cystic fibrosis, pulmonary fibrosis, adult respiratory distress

syndrome, rhinitis and asthma in a mammal in need of such treatment, comprising administering at least one compound of formula I or a pharmaceutically acceptable salt thereof to a patient.

The term "treatment" as used herein includes curative treatment and prophylactic treatment. By "curative" treatment is meant efficacy in treating a current symptomatic episode of a disorder or condition. By "prophylactic" treatment is meant prevention of the occurrence or recurrence of a disorder or condition.

For treating diseases, compounds of formula I, or their pharmaceutically acceptable salts, may be employed at an effective daily dosage and administered in the form of a pharmaceutical composition.

Therefore, another embodiment of the present invention concerns a pharmaceutical composition comprising an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof in combination with a pharmaceutically acceptable diluent or carrier.

To prepare a pharmaceutical composition according to the invention, one or more of the compounds of formula I or a pharmaceutically acceptable salt thereof, is intimately admixed with a pharmaceutical diluent or carrier according to conventional pharmaceutical techniques known to the skilled practitioner.

Pharmaceutical compositions comprising compounds according to the invention can, for example, be administered orally or parenterally, i. e. , intravenously, intramuscularly, subcutaneously or by inhalation (orally or intranasally). In a preferred embodiment, the pharmaceutical compositions are administered by inhalation.

Pharmaceutical compositions suitable for oral administration can be solids or liquids and can, for example, be in the form of tablets, pills, dragees, gelatin capsules,

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solutions, syrups, aerosols, powders for inhalation and the like. Pharmaceutical compositions suitable for administration by inhalation are preferred.

The following examples are provided for illustrative purposes.

Unless otherwise specified in the examples, characterization of the compounds was performed according to the following methods:

NMR spectra are recorded on a BRUKER AC 250 Fourier Transform NMR Spectrometer fitted with an Aspect 3000 computer and a 5 mm $^1\text{H}/^{13}\text{C}$ dual probehead or BRUKER DRX 400 FT NMR fitted with a SG Indigo2 computer and a 5 mm inverse geometry $^1\text{H}/^{13}\text{C}/^{15}\text{N}$ triple probehead. The compound is studied in DMSO-d_6 (or CDCl_3) solution at a probe temperature of 313 K and at concentrations ranging from 2 to 20 mg/ml. The instrument is locked on the deuterium signal of DMSO-d_6 (or CDCl_3). Chemical shifts are given in ppm downfield from TMS taken as internal standard.

Mass spectrometric measurements in LC/MS mode are performed as follows:

HPLC conditions

Analyses are performed using a WATERS Alliance HPLC system mounted with an INERTSIL ODS 3-, DP 5Am, 250 X 4.6 mm column.

The gradient runs from 100 % solvent A (acetonitrile, water, TFA (10/90/0.1, v/v/v)) to 100 % solvent B (acetonitrile, water, TFA (90/10/0.1, v/v/v)) in 7 min with a hold at 100 % B of 4 min. The flow rate is

set at 2.5 ml/min and a split of 1/10 is used just before API source. The chromatography is carried out at 30 C.

MS conditions

Samples are dissolved in acetonitrile/water, 70/30, v/v at the concentration of about 250 µg/ml. API spectra (+ or-) are performed using a FINNIGAN (San Jose, CA, USA) LCQ ion trap mass spectrometer. APCI source operates at 450 C and the capillary heater at 160 C. ESI source operates at 3.5 kV and the capillary heater at 210 C.

Mass spectrometric measurements in EI/DIP mode are performed as follows: samples are vaporized by heating the probe from 50 C to 250 C in 5 min. EI (Electron Impact) spectra are recorded using a FINNIGAN (San Jose, CA, USA) TSQ 700 tandem quadrupole mass spectrometer. The source temperature is set at 150 C.

Specific rotation is recorded on a Perkin-Elmer MC241 or MC341 polarimeter.

The angle of rotation is recorded at 25 C on 1 % solutions in MeOH. For some molecules, the solvent is CH₂Cl₂ or DMSO, due to solubility problems.

Water content is determined using a Metrohm microcoulometric Karl Fischer titrator.

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Preparative chromatographic separations are performed on silicagel 60 Merck, particle size 15-40 µm, reference 1.15111.9025, using in-house modified Jobin Yvontype axial compression columns (80 mm i. d.), flow rates between 70 and 150 ml/min.

Amount of silicagel and solvent mixtures are as described in individual procedures.

Preparative chiral chromatographic separations are performed on a DAICEL Chiralpak AD20Am, 100*500 mm column using an in-house build instrument with various mixtures of lower alcohols and C5 to C8 linear, branched or cyclic alkanes at 350 ml/min. Solvent mixtures are as described in individual procedures.

Melting points are determined on a Bchi 535 or 545 Tottoli-type fusionometre, and are not corrected, or by the onset temperature on a Perkin Elmer DSC 7.

Unless specified otherwise in the examples, the compounds are obtained in the neutral form.

In the tables, the stereochemical information is contained in the three columns headed 'configuration data'. The second column indicates whether a compound has no stereogenic center (ACHIRAL), is a pure configuration isomer or enantiomer (PURE), a racemate (RAC) or is a mixture of two or more stereoisomers, possibly in unequal proportions (MIXT). The first column contains the stereochemical assignment for each recognised center, following the IUPAC numbering used in the preceding column. A number alone indicates the existence of both configurations at that center. A number followed by 'R' or 'S' indicates the known absolute configuration at that center. A number followed by '*' indicates the existence of only one but unknown absolute configuration at that center. The letter (A, B, C, D) in front is a way of distinguishing the various configuration isomers, enantiomers or racemates of the same structure.

The third column precises the cis or trans isomerism.

In the tables, the melting points are in most cases determined by the onset of the DSC curve. When a visual (fusionometer) melting point is given, the value is between brackets.

EXAMPLE 1 : Synthesis of amidines of formula VII.

1. 1 Synthesis of 2-methylcyclopropanecarbonitrile 1. EMI29.1

To a suspension of sodium hydride (11 g, 0.28 mol, 60 % in oil, washed two times with n-hexane) in tetrahydrofuran (150ml) is added diethyl cyanomethylphosphonate (45.5 g, 0.25 mol) over 0.5 h, at room temperature. The mixture is stirred 0.25 h. Propylene oxide (16.3 g, 0.28 mol) is added dropwise at room temperature and the solution is stirred for 1 h then heated at reflux for 4 h. The

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mixture is cooled and ammonium chloride (115g) is added. The solvent is distilled, the residue is poured onto crushed ice and extracted three times with diethyl ether. The combined organic layers are washed with brine, dried over magnesium sulfate, concentrated (atmospheric pressure) and the final residue is distilled under reduced pressure (75 C, 70 mmHg) to afford pure 2-methylcyclopropanecarbonitrile 1 (7.5 g, 33 %) as an oil.

1.2 Synthesis of 2-methylcyclopropanecarboximidamide hydrochloride 2. EMI30.1

Gaseous hydrochloric acid is passed through a solution of 2-methylcyclopropanecarbonitrile 1 (7.5 g, 92 mmol) in ethanol (8.5ml) at 0 C until 7 g have been absorbed. The resulting mixture is kept in the refrigerator for 48 h. Ethanol (150 ml) is then added and gaseous ammonia is passed through the solution at -5 C for 4 h. The solvent is evaporated in vacuo. Hydrochloric acid in diethyl ether (3 N solution, 3 ml) is added and the solution is concentrated and dried in vacuo to afford 2-methylcyclopropanecarboximidamide hydrochloride 2 (6.15 g, 50 %) as a paste that is used without further purification.

EXAMPLE 2: synthesis of 4,6-pyrimidinediol derivatives of formula VI.

2.1 Synthesis of 2-cyclopropyl-5-fluoro-4, 6-pyrimidinediol 3. EMI30.2

Sodium (646 mg, 28 mmol) is dissolved in methanol (50ml) under a nitrogen atmosphere. Cyclopropanecarboximidamide hydrochloride (3.40 g, 28 mmol) is added in one portion. The mixture is stirred at room temperature for 0.25 h, then filtered upon hyflocel. The filtrate is concentrated in vacuo. This free base is added to a solution of sodium (1.29 g, 56 mmol) in methanol (50 ml) under a nitrogen atmosphere, at room temperature. Diethyl fluoromalonate (5 g, 28 mmol) is added and the mixture is stirred at 60 C for 5 h. The solvent is evaporated and the yellowish solid obtained is dissolved in 60ml of water. The pH is adjusted at 6 with a 5 N HCl solution and the white precipitate formed is filtered and dried. 2-cyclopropyl-5-fluoro- 4,6-pyrimidinediol 3 (3.6 g, 76 %) is

obtained as a white powder and used in the next step without further purification.

¹H NMR (250 MHz, DMSO): 0.95 (m, 4H), 1.83 (m, 1H), 12.1 (bs, 2H).

<Desc/Clms Page number 31>

Compounds described in table 1 can be synthesized in an analogous way.

Table 1
EMI31.1

<tb> 4 <SEP> 2-cyclopropyl-4,6-pyrimidinediol <SEP> Patent <SEP> Geigy <SEP> 1966, <SEP> NL6513321
<tb>
<tb> 5 <SEP> 2-cyclopropyl-5-methyl-4, <SEP> 6- <SEP> MS <SEP> (M+#) <SEP> : <SEP> 166
<tb>
<tb> <SEP> pyrimidinediol
<tb>
<tb> 6 <SEP> 5-chloro-2-cyclopropyl-4, <SEP> 6- <SEP> MS <SEP> (M+#) <SEP> : <SEP> 187/189
<tb>
<tb> <SEP> pyrimidinediol
<tb>
<tb> 7 <SEP> 2-cyclopropyl-5-methoxy-4, <SEP> 6- <SEP> MS <SEP> (M+#) <SEP> : <SEP> 182
<tb>
<tb> <SEP> (midinediol
<tb>
<tb> 8 <SEP> 2-cyclopropyl-5-ethyl-4, <SEP> 6- <SEP> MS <SEP> (M+-) <SEP> : <SEP> 180
<tb>
<tb> <SEP> pyrimidinediol
<tb>
<tb> 9 <SEP> 2-(2-methylcyclopropyl)-4,6- <SEP> ¹ H <SEP> NMR <SEP> (250 <SEP> MHz, <SEP> DMSO): <SEP> 0. <SEP> 83 <SEP> (m, <SEP> 1H),
<tb>
<tb> <SEP> pyrimidinediol <SEP> 1. <SEP> 11 <SEP> (d, <SEP> 3H), <SEP> 1. <SEP> 18 <SEP> (m, <SEP> 1H), <SEP> 1. <SEP> 38 <SEP> (m, <SEP> 1H),
<tb>
<tb> <SEP> 1.61 <SEP> (m, <SEP> 1H), <SEP> 5.03 <SEP> (s, <SEP> 1H)
<tb>
<tb> 10 <SEP> 5-methyl-2- <SEP> (2-methylcyclopropyl)- <SEP> MS <SEP> (MH+): <SEP> 181
<tb>
<tb> <SEP> 4, <SEP> 6-pyrimidinediol
<tb>
<tb> 11 <SEP> 2- <SEP> (cyclopropylmethyl)-5-methyl- <SEP> MS <SEP> (MH+): <SEP> 181
<tb>
<tb> <SEP> 4,6-pyrimidinediol
<tb>
<tb> 12 <SEP> 2-cyclobutyl-5-methyl-4, <SEP> 6-MS <SEP> (M+-) <SEP> : <SEP> 180
<tb>
<tb> <SEP> pyrimidinediol
<tb>
<tb> 13 <SEP> 2-isopropyl-5-methyl-4, <SEP> 6- <SEP> MS <SEP> (MH+): <SEP> 169

<tb>
 <tb> <SEP> pyrimidinediol
 <tb>
 <tb> 14 <SEP> 2-cyclopentyl-5-methyl-4, <SEP> 6- <SEP> MS <SEP> (M+#) <SEP> : <SEP> 194
 <tb>
 <tb> <SEP> imidinediol
 <tb>
 <tb> 15 <SEP> [3-(2-cyclopropyl-4,6-dihydroxy- <SEP> MS <SEP> (MH+): <SEP> 310
 <tb>
 <tb> <SEP> pyrimidin-5-yl)-propyl]-carbamic
 <tb>
 <tb> <SEP> acid <SEP> ter-butyl <SEP> ester
 <tb>
 <tb> 16 <SEP> [4- <SEP> (2-cyclopropyl-4, <SEP> 6-dihydroxy- <SEP> MS <SEP> (MH+): <SEP>
 324
 <tb>
 <tb> <SEP> pyrimidin-5-yl)-butyl]-carbamic
 <tb>
 <tb> <SEP> acid <SEP> ter-butyl <SEP> ester
 <tb>
 2.2 Synthesis of 2-cyclopropyl-5-nitro-4, 6-pyrimidinediol 17.
 EMI31.2

<Desc/Clms Page number 32>

Glacial acetic acid (90 ml) is added to fuming nitric acid (40ml) at 0 C. The solution is warmed to 30 C and 2-cyclopropyl-4,6-pyrimidinediol 4 (35 g, 0.25 mol) is added in portions. The temperature is kept between 30 and 40 C. After 1 h, the mixture is poured onto crushed ice and filtered. The filtrate is concentrated to 50 ml in vacuo. Methanol is added and the precipitate is filtered and dried. Pure 2-cyclopropyl-5-nitro-4, 6-pyrimidinediol 17 (39.8 g, 81 %) is obtained and used in the next step without further purification.

MS(M+·) : 197.

EXAMPLE 3: synthesis of 4,6-dichloropyrimidine derivatives of formula IV.

3.1 Synthesis of 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine 18:

EMI32.1

2-cyclopropyl-5-fluoro-4, 6-pyrimidinediol 3 (3.51 g, 21 mmol) is suspended in phosphorus oxychloride (15 ml). A mixture of N, N-diethylaniline (3.08 g, 21 mmol) and phosphorus oxychloride (15 ml) is added dropwise to the suspension at 0 C. The resulting mixture is stirred at 110 C for 2 h, then cooled to room temperature. The brown solution is poured onto crushed ice and extracted five times with dichloromethane. The combined organic layers are washed three times with a 1 N HCl solution, dried over magnesium sulfate and concentrated in vacuo to afford 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine 18 as an orange oil (4.80 g, 100 %) which is used in the next step without further purification.

MS(M+·) : 205/207/209.

Compounds described in table 2 can be synthesized in an analogous way.

<Desc/Cls Page number 33>

Table2
EMI33.1

<tb>
<tb>
<tb> 19 <SEP> 4, <SEP> 6-dichloro-2-cyclopropylpyrimidine <SEP> MS <SEP> (M+.) <SEP> :
<SEP> 189/191/193
<tb>
<tb>
<tb>
<tb>
<tb>
<tb>
<tb> 20 <SEP> 4, <SEP> 6-dichloro-2-cyclopropyl-5- <SEP> MS <SEP> (M+#) <SEP> : <SEP>
202/204/206
<tb>
<tb>
<tb>
<tb>
<tb>
<tb> <SEP> methylpyrimidine
<tb>
<tb>
<tb>
<tb>
<tb>
<tb> 21 <SEP> 4,5, <SEP> 6-trichloro-2- <SEP> MS <SEP> (M+#) <SEP> : <SEP> 222/224/226
<tb>
<tb>
<tb>
<tb>
<tb>
<tb>
<tb> <SEP> cyclopropylpyrimidine
<tb>
<tb>
<tb>
<tb>
<tb>
<tb> 22 <SEP> 4, <SEP> 6-dichloro-2-cyclopropyl-5- <SEP> MS <SEP> (M+#) <SEP> : <SEP>
218/220/222
<tb>
<tb>
<tb>

<tb>
 <tb>
 <tb> <SEP> 'midin <SEP> 1 <SEP> meth <SEP> 1 <SEP> ether
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb> 23 <SEP> 4, <SEP> 6-dichloro-2-cyclopropyl-5- <SEP> 1H <SEP> NMR <SEP> (250 <SEP>
 MHz, <SEP> CDC13) <SEP> : <SEP> 1.12 <SEP> (m, <SEP> 4H),
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb> <SEP> ethylpyrimidine <SEP> 1. <SEP> 20 <SEP> (t, <SEP> 3H), <SEP> 2.16 <SEP> (m,
 <SEP> 1H), <SEP> 2. <SEP> 85 <SEP> (q, <SEP> 2H)
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb> 24 <SEP> 4, <SEP> 6-dichloro-2-(2- <SEP> eb. <SEP> = <SEP> 85 C/1 <SEP> mmHg
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb> <SEP> meth <SEP> lc <SEP> clo <SEP> ro <SEP> 1)'midine
 <tb>
 <tb>
 <tb>
 <tb>
 <tb>
 <tb> 25 <SEP> 4, <SEP> 6-dichloro-5-methyl-2-(2- <SEP> MS <SEP> (M+#) <SEP> : <SEP>
 216/218/220
 <tb>
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 <tb>
 <tb>
 <tb> <SEP> methylcyclopropyl) <SEP> pyrimidine
 <tb>
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 <tb>
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 <tb>
 <tb> 26 <SEP> 4, <SEP> 6-dichloro-2- <SEP> (cyclopropylmethyl)-5- <SEP> MS <SEP> (MH+):

<SEP> 217/219/221

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> <SEP> methylpyrimidine

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> 27 <SEP> 4, <SEP> 6-dichloro-2-cyclobutyl-5- <SEP> MS <SEP> (MH+): <SEP> 216/218/220

<tb>

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<tb>

<tb>

<tb>

<tb> <SEP> methylpyrimidine

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> 28 <SEP> 4,6-dichloro-2-cyclopentyl-5- <SEP> MS <SEP> (M+#) <SEP> : <SEP> 233/235/237

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> <SEP> nitropyrimidine

<tb>

<tb>

<tb>

<tb>

<tb>

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<tb> 29 <SEP> 4, <SEP> 6-dichloro-2-cyclopentyl-5- <SEP> MS <SEP> (M+#) <SEP> : <SEP>
204/206/208

<tb>

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<tb> <SEP> methylpyrimidine

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> 30 <SEP> 4, <SEP> 6-dichloro-2-cyclopentyl-5- <SEP> MS <SEP> (M+#) <SEP> : <SEP>
230/232/234

<tb>

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> <SEP> methylpyrimidine

<tb>

EXAMPLE 4: synthesis of compounds of formula II and II-A.

4.1 Synthesis of 6-chloro-N, 2-dicyclopropyl-5-fluoro-4-pyrimidinamine 31.

EMI33.2

Cyclopropylamine (11.4 g, 0.200 mol) is added to 4,6-dichloro-2-cyclopropyl-5-fluoropyrimidine 18 (4.80 g, 23 mmol) and the solution is stirred at room temperature for 1 h. The mixture is diluted with diethylether, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford 6-chloro-N, 2-dicyclopropyl-5-fluoro-4-

<Desc/Clms Page number 34>

pyrimidinamine 31 as a yellow oil (4.99 g, 95 %) which is used in the next step without further purification.

MS(M+-) : 227/229.

Compounds described in table 3 can be synthesized in an analogous way.

<Desc/Clms Page number 35>

Table 3

EMI35.1

<tb>

<tb>

<tb> 32 <SEP> 6-chloro-N, <SEP> 2-dicyclopropyl-4-'midinamine <SEP> MS <SEP> (MH+): <SEP>
210/212

<tb>

<tb>

<tb>

<tb>

<tb>

<tb> 33 <SEP> 6-chloro-N, <SEP> 2-dicyclopropyl-5-methyl-4- <SEP> MS <SEP> (MH+): <SEP>
223/225

<tb>

<tb>

<tb>
<tb>
<tb>
<tb> <SEP> imidinamine
<tb>
<tb>
<tb>
<tb>
<tb> 34 <SEP> 5,6-dichloro-N, <SEP> 2-dicyclopropyl-4-pyrimidinamine <SEP> MS <SEP> (MH+)
<SEP> : <SEP> 244/246/248
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<tb>
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<tb>
<tb> 35 <SEP> 6-chloro-N, <SEP> 2-dicyclopropyl-5-methoxy-4- <SEP> MS <SEP> (MH+): <SEP>
240/242
<tb>
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<tb> <SEP> pyrimidinamine
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<tb>
<tb>
<tb>
<tb> 36 <SEP> 6-chloro-N, <SEP> 2-dicyclopropyl-5-ethyl-4- <SEP> MS <SEP> (MH+): <SEP>
238/240
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<tb> <SEP> 'diamine
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<tb> 37 <SEP> N-[6-chloro-2-(2-trans-methylcyclopropyl)-4- <SEP> MS <SEP> (MH+): <SEP>
224/226
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(MH+): <SEP> 238/240
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255/257
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238/240
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<Desc/Clms Page number 36>

(i) compound 37 was resolved into its enantiomers 38 (first eluted) and 39 (second eluted) by chromatography on a chiral support (Daicel Chiralpak AD, isopropanol/n-hexane 1/99, 20 °C).

4.2 Synthesis of 4-chloro-2-cyclopropyl-6- (3-fluoro-azetidin-1-yl)-pyrimidine 163.

4.2. 1 Synthesis of 1-benzhydryl-3-fluoroazetidine 161.
 EMI36.1

A solution of N-tetrabutylammonium fluoride (1 M solution in THF, 32 ml, 32 mmol) is added dropwise to a solution of methanesulfonic acid 1-benzhydryl-azetidin-3-yl ester (10.75 g, 32 mmol) in acetonitrile (250 ml). The solution is refluxed for 30 hours then concentrated in vacuo. The mixture is diluted with dichloromethane and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford 10.5 g of a crude mixture which is purified by column chromatography (dichloromethane/hexane 3/1) to afford pure 1-benzhydryl-3-fluoroazetidine 161 (4.3 g, 55 %).

* MS (MH⁺): 242.

4.2. 2 Synthesis of 3-fluoroazetidine hydrochloride 162.
 EMI36.2

Palladium on barium sulfate (5 %, 1.5 g) is suspended in methanol (20 ml) under a nitrogen atmosphere. 1-benzhydryl-3-fluoroazetidine 161 (4.3 g, 18 mmol) is added together with water (0.6 ml), methanol (80 ml) and a 3 N hydrochloric acid- methanol solution (16 ml). The mixture is put under a 50 psi hydrogen pressure and heated at 55 °C for 3 days. The catalyst is filtered and the filtrate is concentrated in vacuo. The mixture is diluted with water and washed three times with hexane. The combined aqueous layers are concentrated in vacuo to afford 3-fluoroazetidine hydrochloride 162 (2.1 g, 99 %) which is used in the next step without further purification.

MS (MH⁺): 76.

<Desc/Clms Page number 37>

4.2. 3 Synthesis of 4-chloro-2-cyclopropyl-6- (3-fluoro-azetidin-1-yl)-pyrimidine 163. EMI37.1

A mixture of 4,6-dichloro-2-cyclopropylpyrimidine 19 (1.05 g, 5.5 mmol), 3-fluoroazetidine hydrochloride 162 (0.68 g, 6 mmol) and potassium carbonate (2.48 g, 18 mmol) in 1-methoxy-2-propanol (10 ml) is heated at 65 °C for 2 hours. The mixture is cooled, concentrated in vacuo, diluted with dichloromethane and washed three times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford 4-chloro-2-cyclopropyl-6- (3-fluoro-azetidin-1-yl)-pyrimidine 163 (1.16 g, 92 %) as a yellow oil which is used in the next step without further purification.

MS (MH⁺): 228/230.

Compounds described in table 4 can be synthesized according to this method.

Table 4:
EMI37.2

<tb> <SEP> IUPAC <SEP> NAME <SEP> MS <SEP> (LC-MS)
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<tb>
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<tb> <SEP> azetidiny)pyrimidine
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<tb> <SEP> azetidiny) <SEP> pyrimidine
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<tb> <SEP> methylpyrimidine
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<tb> <SEP> methylpyrimidine

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<Desc/Clms Page number 38>

EXAMPLE 5: synthesis of 4-hydroxypyrimidines of formula XII 5.1 Synthesis of 2-cyclopropyl-6,7-dihydro-5H-pyrrolo [2, 3-d] pyrimidin-4-ol 48.

EMI38.1

Sodium (0.417 g, 18.1 mmol) is dissolved in methanol (65ml) under a nitrogen atmosphere. Cyclopropanecarboximidamide hydrochloride (2.19 g, 18.1 mmol) is added in one portion. The mixture is stirred at room temperature for 0.25 h, then filtered upon hyflocel. The filtrate is concentrated in vacuo to 30ml. This free base is added to a solution of sodium (0.834 g, 36.2 mmol) in methanol (130ml) under a nitrogen atmosphere, at room temperature. 2-ethoxy-4,5-dihydro-3H-pyrrole-3- carboxylic acid ethyl ester (3.4 g, 18.1 mmol) in methanol is added and the mixture is stirred at 60 C overnight. After cooling, the solvent is evaporated and the solid obtained is dissolved in water. The pH is adjusted at 5 with a 5 N HCl solution and the white precipitate formed is filtered and dried. 2-cyclopropyl-6,7-dihydro-5H-pyrrolo [2,3-d] pyrimidin-4-ol 48 (1.88 g, 59 %) is obtained as a white powder and used in the next step without further purification.

MS (MH⁺): 178.

EXAMPLE 6: synthesis of 4-chloropyrimidines of formula X.

6.1 Synthesis of 4-chloro-2-cyclopropyl-5,6, 7,8-tetrahydro-5H-pyrido [2,3-d]pyrimidine 50.

EMI38.2

[3-(2-cyclopropyl-4, 6-dihydroxy-pyrimidin-5-yl)-propyl]-carbamic acid tert-butyl ester 15 (1.4 g, 4.5 mmol) is suspended in phosphorus oxychloride (10 ml). A mixture of N, N-diethylaniline (0.744 g, 5 mmol) and phosphorus oxychloride (10 ml) is added dropwise to the suspension at room temperature. The resulting mixture is stirred at 100 C overnight. The solution is poured onto crushed ice and extracted two times with dichloromethane. The aqueous layer is alkalized using a saturated sodium hydrogenocarbonate solution (pH 8), extracted two times with dichloromethane, reacidified using HCl 5N (pH 3) and extracted again with dichloromethane. The combined aqueous layers are alkalized (pH 10) and the white

<Desc/Clms Page number 39>

precipitate formed is filtered and dried. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford a mixture of 4-chloro-2-cyclopropyl-5,6, 7,8-tetrahydro-5H-pyrido [2, 3-d] pyrimidine 50 and non-cyclized 3- (4, 6-dichloro-2-cyclopropyl-pyrimidin-5-yl)propylamine 49. This mixture is dissolved in 1-methoxy-2-propanol and heated at 140 C for 5 h. After cooling, the solution is diluted with dichloromethane and washed with water (2x) and with an hydrochloric acid solution (1 N). The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The resulting crude mixture is purified by chromatography on silica gel preparative plates (dichloromethane/ethanol/ammonia 97/3/0.3) to afford a solid, which is combined with the first-formed precipitate. Pure 4-chloro-2-cyclopropyl-5,6, 7, 8-tetrahydro-5H-pyrido [2,3-d] pyrimidine 50 is obtained as an orange solid (209 mg, 20 %).

MS (MH⁺): 210/212.

4-chloro-2-cyclopropyl-6,7, 8, 9-tetrahydro-5H-pyrimido [4,5-b] azepine 51 can be synthesized in an analogous way.

MS (MH⁺): 224/226 6.2 Synthesis of 4-chloro-2-cyclopropyl-6,7-dihydro-5H-pyrrolo [2, 3-d] pyrimidine
EMI39.1

48 52

2-cyclopropyl-6,7-dihydro-5H-pyrrolo [2,3-d]pyrimidin-4-ol 48 (0.5 g, 2.8 mmol) is suspended in phosphorus oxychloride (0.7 ml). A mixture of N, N-diethylaniline (0.46 g, 3.1 mmol) and phosphorus oxychloride (0.7ml) is added dropwise to the suspension at room temperature. The resulting mixture is stirred at 120 C for 3 h. The solution is poured onto crushed ice and extracted two times with dichloromethane. The aqueous layer is alkalized (pH 10) and extracted four times with dichloromethane. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo.

The crude mixture (370 mg, 68 %, 91 % purity) is used in the next step without further purification due to the instability of the compound.

MS (MH⁺): 196/198

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EXAMPLE 7: synthesis of compounds of formula I.

7.1 Synthesis of N, 2-dicyclopropyl-5-fluoro-6- (4-thiomorpholinyl)-4- pyrimidinamine 120.
EMI40.1

A mixture of thiomorpholine (2.27 g, 22 mmol) and 6-chloro-N, 2-dicyclopropyl-5-fluoro-4-pyrimidinamine 31 (1 g, 4.4 mmol) is stirred at 110 C for 18 hours. After cooling, the brown solution is diluted with dichloromethane, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil. The crude oil is purified by column chromatography (hexane/ethyl acetate: 80/20) to give N,2-dicyclopropyl-5-fluoro-6- (4-thiomorpholinyl)-4-pyrimidinamine 120 (915 mg, 71 %) as a yellowish solid.

7.2 Synthesis of N4-cyclohexyl-N6, 2-dicyclopropyl-5-methyl-4, 6-pyrimidinediamine 141.
EMI40.2

A mixture of cyclohexylamine (1.78 g, 18 mmol) and 6-chloro-N, 2-dicyclopropyl-5-methyl-4-pyrimidinamine 33 (0.70 g, 3 mmol) in 1-methoxy-2-propanol (2ml) is stirred at 125 C for 120 hours. After cooling, the brown solution is diluted with dichloromethane, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil. The crude oil is purified by column chromatography (dichloromethane/methanol: 97.3/2.7) to give pure N4-cyclohexyl-N6, 2-dicyclopropyl-5-methyl-4, 6-pyrimidinediamine 141 (0.150 g, 17 %).

<Desc/Clms Page number 41>

7.3 Synthesis of 6- (1-azepanyl)-N4, 2-dicyclopropyl-4, 5-pyrimidinediamine 63. EMI41.1

6- (1-azepanyl)-N, 2-dicyclopropyl-5-nitro-4-pyrimidinamine 197 was synthesized as described in 7.1 using 6-chloro-N, 2-dicyclopropyl-5-nitro-4-pyridinamine 44 and azepane as starting material.

MS (MH⁺): 318.

To a suspension of 6- (1-azepanyl)-N, 2-dicyclopropyl-5-nitro-4-pyrimidinamine 197 (0.5 g, 16 mmol) in 1,4-dioxane (35 ml) and water (35 ml) is added sodium hydrosulfite (2.19 g, 13 mmol) and ammonia (25 % solution, 1.2 ml). The mixture is stirred at room temperature for 10 h then diluted with ethyl acetate and washed three times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford a yellow oil. The crude oil is purified by column chromatography (dichloromethane/ethanol/ammonia : 95/5/0.5) to give pure 6- (1-azepanyl)-N4,2-dicyclopropyl-4, 5-pyrimidinediamine 63 (137 mg, 30 %) as a reddish solid.

7.4 Synthesis of 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4- piperidinone hydrate 107. EMI41.2

A solution of 1 NHC1 (15 ml) is added to a solution of N, 2-dicyclopropyl-6- (1, 4-dioxa-8-azaspiro [4.5]dec-8-yl)-5-methyl-4-pyrimidinamine 149 (285 mg, 0.86 mmol) in tetrahydrofuran (15 ml). The mixture is stirred at room temperature for 18 h, then diluted with dichloromethane and washed three times with sodium bicarbonate. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford a white paste. The compound is dried under vacuum to give pure 1- [2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-4-piperidinone hydrate 107 (160 mg, 61 %) as a white paste.

<Desc/Clms Page number 42>

7.5 Synthesis of 6-azepan-1-yl-5-bromo-N, 2-dicyclopropylpyrimidin-4-amine 61. EMI42.1

N-Bromosuccinimide (0.39 g, 2.2 mmol) is added to a solution of 6- (1-azepanyl)-N,2-dicyclopropyl-4-pyrimidinamine 62 (0.5 g, 1.84 mmol) in chloroform (2 ml). The mixture is stirred at 60 °C overnight then cooled, diluted with dichloromethane and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo. The crude mixture is purified by column chromatography (dichloromethane/ethanol : 97/3) to give pure 6-azepan-1-yl-5-bromo-N, 2-dicyclopropylpyrimidin-4-amine 61 (134 mg, 21 %) as a brownish paste.

7.6 Synthesis of 4-azepan-1-yl-2-cyclopropyl-5, 6,7,8-tetrahydro-pyrido [2,3- d]pyrimidine 155.

EMI42.2

A mixture of azepane (18.2ml, 142 mmol) and 4-chloro-2-cyclopropyl-5,6,7,8-tetrahydro-5H-pyridol2,3-dlpyrimidine 50 (0.851g, 4.06 mmol) is stirred four days at 110 °C. After cooling, the brown solution is diluted with dichloromethane and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil. The crude oil is purified by column chromatography (dichloromethane/ethanol/ammonia : 90/10/1) to give pure 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido [2,3-d] pyrimidine 155 as a brown solid.

7.7 Synthesis of 1-[2-cyclopropyl-6-(3-fluoro-azetidin-1-yl)-pyrimidin-4-yl] azepane fumarate (3:2) 195.

EMI43.1

A mixture of hexamethyleneimine (2.87 g, 29 mmol) and 4-chloro-2-cyclopropyl-6-(3-fluoro-azetidin-1-yl)-pyrimidine 163 (1.1 g, 4.8 mmol) in 1-methoxy-2-propanol (2ml) is stirred at 110 °C for 6 hours. After cooling, the solution is diluted with dichloromethane, washed two times with a saturated sodium bicarbonate solution. The combined organic layers are dried over magnesium sulfate and concentrated under high vacuum to afford a brown oil (2.15g). The crude oil is purified by column chromatography (dichloromethane/methanol 99.5/0.5) to give pure 1-[2-cyclopropyl-6-(3-fluoro-azetidin-1-yl)-pyrimidin-4-yl]azepane (1 g, 72 %).

MS(MH⁺) : 291.

A solution of fumaric acid (0.6g) in isopropanol (4 ml) is added to a solution of 1-[2-cyclopropyl-6-(3-fluoro-azetidin-1-yl)-pyrimidin-4-yl] azepane in diisopropyl ether (10 ml). The mixture is triturated, then filtered, recrystallized from diisopropyl ether and dried in vacuo to afford pure 1-[2-cyclopropyl-6-(3-fluoro-azetidin-1-yl)-pyrimidin-4-yl] azepane fumarate (3:2) 195 (1.2 g, 58%).

MS(MH⁺) : 291.

7.8 Synthesis of methanesulfonic acid 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-yl ester 190.

EMI43.2

A solution of methanesulfonyl chloride (0.63ml, 7.6 mmol) in dichloromethane (10ml) is added dropwise to a solution of 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-ol 189 (1.90g, 6.3 mmol) and triethylamine (1.74ml, 13 mmol) in dichloromethane (90ml) at 0 °C. The mixture is stirred 1 hour at 0 °C and 1 hour at room temperature. Water (40ml) is added and the mixture is extracted three times with dichloromethane. The combined organic layers are dried over magnesium

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sulfate and concentrated in vacuo to afford pure methanesulfonic acid 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-yl ester 190 (2.66 g, 100%).

MS (MH⁺) : 381.

7.9 Synthesis of 1-[6-(3-bromo-azetidin-1-yl)-2-cyclopropyl-5-methyl-pyrimidin-4-yl]-azepane 182.
EMI44.1

A mixture of methanesulfonic acid 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-yl ester 190 (0.4 g, 1 mmol) and sodium bromide (0.103 g, 1 mmol) in N,N-dimethylformamide (10 ml) is heated at 100 °C for 6 days. The mixture is then cooled and concentrated in vacuo. The mixture is diluted with dichloromethane and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford 0.4 g of a crude mixture, which is purified by column chromatography (dichloromethane/methanol 98/2). 1-[6-(3-bromo-azetidin-1-yl)-2-cyclopropyl-5-methyl-pyrimidin-4-yl]-azepane 182 (0.11 g, 30 %) is obtained.

MS(MH⁺) : 365/367.

7.10 Synthesis of 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidine-3-carbonitrile 183.
EMI44.2

A mixture of methanesulfonic acid 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-yl ester 190 (0.3 g, 0.8 mmol) and sodium cyanide (0.047 g, 1.0 mmol) in N,N-dimethylformamide (5 ml) is heated at 120 °C for 24 hours. The mixture is then cooled and concentrated in vacuo. The mixture is diluted with dichloromethane and washed two times with water. The combined organic layers are

<Desc/Clms Page number 45>

dried over magnesium sulfate and concentrated in vacuo to afford 0.4 g of a crude mixture, which is purified by column chromatography (dichloromethane/ethanol 98/2). 0.10 g (60 %) of 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidine-3-carbonitrile 183 is obtained.

MS(MH⁺) : 312.

7.11 Synthesis of 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-one 193.
EMI45.1

A solution of sulfur trioxide/pyridine complex (1.4 g, 8.8 mmol) in DMSO (3.5 ml) is added dropwise to a solution of 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-ol 189 (0.3 g, 0.7 mmol) and triethylamine (1 ml) in DMSO (7 ml). The mixture is stirred at room temperature for 24 hours, poured onto ice, diluted with ethyl acetate and washed two times with water. The combined organic layers are dried over magnesium sulfate and concentrated in vacuo to afford 0.4 g (96%) of pure 1-(6-azepan-1-yl-2-cyclopropyl-5-methyl-pyrimidin-4-yl)-azetidin-3-one hydrate 193.

MS (MH⁺) : 319.

Compounds described in table 5 can be synthesized according to one of these methods.

<Desc/Clms Page number 46>

Table 5
EMI46.1

Salt/solvate Configuration data Free base IUPAC NAME MH+ (M+#) DSC C (mp) alphaD

53 1 HCl achiral N,2-dicyclopropyl-6-(1,3-thiazolidin-3-yl)-4-pyrimidinamine (262) 181.3

54 1 HCl achiral N-cyclopropyl-2-isopropyl-6-[1,3-thiazolidin-3-yl)-4- (264) 204.4
pyrimidinamine

55 1 maleate achiral 6-(1-azepanyl)-2-cyclobutyl-N-cyclopropyl-5-methyl-4- 301
pyrimidinamine

56 1 maleate achiral 6-(1-azepanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine 287

57 3/2 achiral 6-(1-azepanyl)-N,2-dicyclopropyl-5-methyl-4-pyrimidinamine <SEP> 287 <SEP> 149.9
<tb> fumarate

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methyl-4- <SEP> 301

<tb> pyrimidinamine

<tb> 59 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 6-(1-azepanyl)-5-chloro-N,2-dicyclopropyl-4-
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351/353

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124.6

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<SEP> (76.9)

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<tb> pyrimidinamine

<tb> 65 <SEP> 1 <SEP> maleate <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> 6-(1-azepanyl)-N-
cyclopropyl-5-methyl-2-(2- <SEP> 301

<tb> methylcyclopropyl)-4-pyrimidinamine

<tb> 66 <SEP> 1 <SEP> maleate <SEP> B-1,2 <SEP> rac <SEP> cis <SEP> 6-(1-azepanyl)-N-
cyclopropyl-5-methyl-2-(2- <SEP> 301

<tb> methylcyclopropyl)-4-pyrimidinamine

<tb>

<Desc/Clms Page number 47>

EMI47.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP>
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<tb> 67 <SEP> B-1,2 <SEP> pure <SEP> trans <SEP> 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-
<SEP> 301 <SEP> -58.79

<tb> methylcyclopropyl)-4-pyrimidinamine

<tb> 68 <SEP> A-1,2 <SEP> pure <SEP> trans <SEP> 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-
 <SEP> 301 <SEP> ~57.65
 <tb> methylcyclopropyl)-4-pyrimidinamine
 <tb> 69 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 6-(1-azepanyl)-N-cyclopropyl-2-
 (cyclopropylmethyl)-5-methyl- <SEP> 301
 <tb> 4-pyrimidinamine
 <tb> 70 <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> 6-(1-azepanyl)-N-cyclopropyl-5-methyl-2-(2-
 <SEP> 321
 <tb> methylcyclopropyl)-4-pyrimidinamine
 <tb> 71 <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> 6-(1-azepanyl)-N-cyclopropyl-2-(2-
 methylcyclopropyl)-4- <SEP> 287
 <tb> pyrimidinamine
 <tb> 72 <SEP> 0.2 <SEP> iPrOH, <SEP> 1 <SEP> achiral <SEP> 6-(1-azocanyl)N,2-dicyclopropyl-5-
 methyl-4-pyrimidinamine <SEP> 301
 <tb> maleate
 <tb> 73 <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> 6-(1-azocanyl)-N-cyclopropyl-2-(2-
 methylcyclopropyl)-4- <SEP> 301 <SEP> 108.5
 <tb> pyrimidinamine
 <tb> 74 <SEP> 3,5 <SEP> mixt <SEP> N,2-dicyclopropyl-6-[3,5-dimethyl-1-piperidinyl]-5-methyl-4-
 <SEP> 301 <SEP> 91.2
 <tb> pyrimidinamine
 <tb> 75 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-6-[4-(2-methoxyphenyl)-1-
 piperidinyl]-5- <SEP> 379 <SEP> 123.6
 <tb> methyl-4-pyrimidinamine
 <tb> 76 <SEP> 1 <SEP> tPrOH, <SEP> 1 <SEP> achiral <SEP> (1-[2-cyclopropyl-6-
 (cyclopropylamino)-5-methyl-4- <SEP> 455 <SEP> 86.1
 <tb> maleate <SEP> pyrimidinyl]-4-piperidinyl](diphenyl)methanol
 <tb> 77 <SEP> achiral <SEP> N,2-dicyclopropyl-5-methyl-6-[4-(trifluoromethyl)piperidin-1-yl] <SEP>
 341 <SEP> (86.4)
 <tb> -4-pyrimidinamine
 <tb>

<Desc/Cls Page number 48>

EMI48.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP>
 NAME <SEP> MH+ <SEP> (M+#) <SEP> DSC <SEP> C <SEP> (mp) <SEP> alphaD
 <tb> 78 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4,4-difluoro-1-
 piperidinyl)-5-methyl-4- <SEP> 309 <SEP> 121.9
 <tb> pyrimidinamine
 <tb> 79 <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4,4-difluoro-1-piperidinyl)-5-methyl-4- <SEP>
 301
 <tb> pyrimidinamine
 <tb> 80 <SEP> 1 <SEP> HCl <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4,4-dimethyl-1-piperidinyl)-
 5-methyl-4- <SEP> 301
 <tb> pyrimidinamine
 <tb> 81 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-
 <SEP> 316 <SEP> 230.6

<tb> 4-piperidinecarboxamide
 <tb> 82 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 6-(4-benzyl-1-piperidinyl)-N,2-dicyclopropyl-5-methyl-4- <SEP> 363 <SEP> 132.1
 <tb> pyrimidinamine
 <tb> 83 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-<SEP> 317 <SEP> 219.6
 <tb> 4-piperidinecarboxylic <SEP> acid
 <tb> 84 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-<SEP> 374 <SEP> 145.3
 <tb> 4-phenyl-4-piperidinecarbonitrile
 <tb> 85 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> ethyl <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4- <SEP> 345 <SEP> 118.9
 <tb> pyrimidinyl]-4-piperidinecarboxylate
 <tb> 86 <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4-ethyl-1-piperidinyl)-5-methyl-4- <SEP> 301
 <tb> pyrimidinamine
 <tb> 87 <SEP> 1 <SEP> HCl <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4-ethyl-1-piperidinyl)-5-methyl-4- <SEP> 301
 <tb> pyrimidinamine
 <tb> 88 <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4-ethyl-4-methyl-1-piperidinyl)-5-methyl- <SEP> 315
 <tb> 4-pyrimidinamine
 <tb>

<Desc/Cls Page number 49>

EMI49.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP> NAME <SEP> MH+ <SEP> (M+#) <SEP> DSC <SEP> C <SEP> (mp) <SEP> alphaD
 <tb> 89 <SEP> 1 <SEP> HCl <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4-ethyl-4-methyl-1-piperidinyl)-5-methyl- <SEP> 315
 <tb> 4-pyrimidinamine
 <tb> 90 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-<SEP> 289 <SEP> 150.0
 <tb> 4-piperidinol
 <tb> 91 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]-<SEP> 365
 <tb> 4-phenyl-4-piperidinol
 <tb> 92 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-fluoro-4-pyrimidinyl]- <SEP> 369
 <tb> 4-phenyl-4-piperidinol
 <tb> 93 <SEP> achiral <SEP> {1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4- <SEP> 303 <SEP> 113.9
 <tb> pyrimidinyl]-4-piperidinyl}methanol
 <tb> 94 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-5-ethyl-6-(4-methyl-1-piperidinyl)-4- <SEP> 301
 <tb> pyrimidinamine
 <tb> 95 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-5-methyl-6-(4-methyl-1-piperidinyl)-4- <SEP> 287 <SEP> 97.9

<tb> pyrimidinamine
 <tb> 95 <SEP> achiral <SEP> N,2-dicyclopropyl-5-fluoro-6-(4-methyl-1-piperidinyl)-4- <SEP> 291
 <tb> pyrimidinamine
 <tb> 97 <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 301 <SEP> 91.3
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 98 <SEP> 1 <SEP> maleate <SEP> B-1,2 <SEP> rac <SEP> cis <SEP> N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 301
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 99 <SEP> A-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 301 <SEP> 61.65
 <tb> piperidinyl)-4-pyrimidinamine
 <tb>

<Desc/Clms Page number 50>

EMI50.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP> NAME <SEP> MH+ <SEP> (M+#) <SEP> DSC <SEP> C <SEP> (mp) <SEP> alphaD
 <tb> 100 <SEP> B-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-5-methyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 301 <SEP> -63.51
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 101 <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 287 <SEP> 120.3
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 102 <SEP> 1 <SEP> HCl <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 287 <SEP> 148.1
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 103 <SEP> 1 <SEP> maleate <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 287 <SEP> 132.1
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 104 <SEP> A-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 287 <SEP> 65.61
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 105 <SEP> B-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-2-(2-methylcyclopropyl)-6-(4-methyl-1- <SEP> 287 <SEP> -70.6
 <tb> piperidinyl)-4-pyrimidinamine
 <tb> 106 <SEP> 1HCl <SEP> achiral <SEP> N,2-dicyclopropyl-5-methyl-6-(4-methylene-1-piperidinyl)-4- <SEP> 285
 <tb> pyrimidinamine
 <tb> 107 <SEP> 1 <SEP> H2O <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methyl-4-pyrimidinyl]- <SEP> 305
 <tb> 4-piperidinone
 <tb> 108 <SEP> achiral <SEP> N4,2-dicyclopropyl-N6,5-dimethyl-N6-[2-(2-thienyl)ethyl]-4,6- <SEP> 329
 <tb> pyrimidinediamine
 <tb> 109 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-5-methyl-N6-[2-(2-thienyl)ethyl]-4,6- <SEP> 315 <SEP> 129.1

<tb> pyrimidinediamine
 <tb> 110 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-N6-[2-furylmethyl)-
 N6,5-dimethyl-4,6- <SEP> 299
 <tb> pyrimidinediamine
 <tb>

<Desc/Clms Page number 51>

EMI51.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP>
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 <tb> 111 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-5-methyl-N6-(2-
 thienylmethyl)-4,6- <SEP> 301 <SEP> 151.9
 <tb> pyrimidinediamine
 <tb> 112 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-5-(3,6-dihydro-1(2H)-
 pyridinyl)-5-methyl-4- <SEP> 271 <SEP> 118.9
 <tb> pyrimidinediamine
 <tb> 113 <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N-cyclopropyl-6-(3,6-dihydro-1(2H)-pyridinyl)-
 2-(2- <SEP> 271 <SEP> 107.4
 <tb> methylcyclopropyl)-4-pyrimidinamine
 <tb> 114 <SEP> 1 <SEP> HCl <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N-cyclopropyl-6-(3,6-
 dihydro-1(2H)-pyridinyl)-2-(2- <SEP> 271
 <tb> methylcyclopropyl)-4-pyrimidinamine
 <tb> 115 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 6-(3-azabicyclo[3.2.1]oct-3-yl)-N,2-
 dicyclopropyl-5-methyl-4- <SEP> 299
 <tb> pyrimidinediamine
 <tb> 116 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-5-methyl-N6-(4-
 pyridinylmethyl)-4,6- <SEP> 296 <SEP> 165.3
 <tb> pyrimidinediamine
 <tb> 117 <SEP> 2 <SEP> maleate <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N4-cyclopropyl-2-(2-
 methylcyclopropyl)-N6-(4- <SEP> 296
 <tb> pyridinylmethyl)-4,6-pyrimidinediamine
 <tb> 118 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-5-ethyl-6-(4-
 thiomorpholinyl)-4- <SEP> 305 <SEP> 99.5
 <tb> pyrimidinediamine <SEP> (1:1)
 <tb> 119 <SEP> 1 <SEP> HCl <SEP> achiral <SEP> N,2-dicyclopropyl-5-methyl-6-(4-
 thiomorpholinyl)-4- <SEP> (290) <SEP> 224.4
 <tb> pyrimidinediamine
 <tb> 120 <SEP> achiral <SEP> N,2-dicyclopropyl-5-fluoro-6-(4-thiomorpholinyl)-4- <SEP> 295
 <SEP> (87)
 <tb> pyrimidinediamine
 <tb> 121 <SEP> achiral <SEP> N,2-dicyclopropyl-6-(4-thiomorpholinyl)-4-pyrimidinamine <SEP>
 (276)
 <tb>

<Desc/Clms Page number 52>

EMI52.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP>
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 <tb> 122 <SEP> achiral <SEP> N,2-dicyclopropyl-5-methoxy-6-(4-thiomorpholinyl)-4- <SEP> 307
 <tb> pyrimidinamine
 <tb> 123 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N-cyclopropyl-2-isopropyl-5-methyl-6-(4-
 thiomorpholinyl)-4- <SEP> 293 <SEP> 89.64
 <tb> pyrimidinamine
 <tb> 124 <SEP> 1 <SEP> HCl <SEP> A-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-5-
 methyl-2-(2-methylcyclopropyl)-6-(4-(304) <SEP> +48.7
 <tb> thiomorpholinyl)-4-pyrimidinamine
 <tb> 125 <SEP> 1 <SEP> HCl <SEP> B-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-5-
 methyl-2-(2-methylcyclopropyl)-6-(4- <SEP> (304) <SEP> -52.0
 <tb> thiomorpholinyl)-4-pyrimidinamine
 <tb> 126 <SEP> 1 <SEP> HCl <SEP> A-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-2-(2-
 methylcyclopropyl)-6-(4-thiomorpholinyl)-4- <SEP> (290) <SEP> +66.9
 <tb> pyrimidinamine
 <tb> 127 <SEP> 1 <SEP> HCl <SEP> B-1,2 <SEP> pure <SEP> trans <SEP> N-cyclopropyl-2-(2-
 methylcyclopropyl)-6-(4-thiomorpholinyl)-4- <SEP> (290) <SEP> -68,6
 <tb> pyrimidinamine
 <tb> 128 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4-benzyl-N6,2-dicyclopropyl-5-methyl-4,6-
 pyrimidinediamine <SEP> 295
 <tb> 129 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4-benzyl-N6,2-dicyclopropyl-N4,5-
 dimethyl-4,6- <SEP> 309 <SEP> 74.5
 <tb> pyrimidinediamine
 <tb> 130 <SEP> 1 <SEP> HBr <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N4-benzyl-N6-
 cyclopropyl-2-(2-methylcyclopropyl)-4,6- <SEP> (294)
 <tb> pyrimidinediamine
 <tb> 131 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-5-methyl-N6-[2-
 (methylsulfanyl)benzyl]- <SEP> 341 <SEP> 132.7
 <tb> 4,6-pyrimidinediamine
 <tb> 132 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-N6-(2,6-difluorobenzyl)-
 5-methyl-4,6- <SEP> 331 <SEP> 162.7
 <tb> pyrimidinediamine
 <tb>

<Desc/Clms Page number 53>

EMI53.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP>
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 <tb> 133 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-N6-(2-fluorobenzyl)-5-
 methyl-4,6- <SEP> 313 <SEP> 141.9
 <tb> pyrimidinediamine
 <tb> 134 <SEP> 1 <SEP> HCl <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N4-cyclopropyl-N6-
 methyl-2-(2-methylcyclopropyl)-N6-(2- <SEP> 354

<tb> nitrobenzyl)-4,6-pyrimidinediamine
 <tb> 135 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4-[3,5-bis(trifluoromethyl)benzyl]-N6,2-dicyclopropyl-5- <SEP> 431 <SEP> 170.8
 <tb> methyl-4,6-pyrimidinediamine
 <tb> 136 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-N6-[3,5-difluorobenzyl]-5-methyl-4,6- <SEP> 331 <SEP> 184.9
 <tb> pyrimidinediamine
 <tb> 137 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4-cycloheptyl-N6,2-dicyclopropyl-5-methyl-4,6- <SEP> 301 <SEP> 136.1
 <tb> pyrimidinediamine
 <tb> 138 <SEP> 1 <SEP> maleate <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N4-cycloheptyl-N6-cyclopropyl-2-(2-methylcyclopropyl)-4,6- <SEP> 301
 <tb> pyrimidinediamine
 <tb> 139 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4-cyclohexyl-N6,2-dicyclopropyl-N4,5-dimethyl-4,6- <SEP> 301 <SEP> (136-137)
 <tb> pyrimidinediamine
 <tb> 140 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 5-chloro-N4-cyclohexyl-N6,2-dicyclopropyl-4,6- <SEP> 307/309 <SEP> 62.9
 <tb> pyrimidinediamine
 <tb> 141 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4-cyclohexyl-N6,2-dicyclopropyl-5-methyl-4,6- <SEP> 287 <SEP> 159.7
 <tb> pyrimidinediamine
 <tb> 142 <SEP> 1 <SEP> maleate <SEP> A-1,2 <SEP> rac <SEP> trans <SEP> N4-cyclohexyl-N6-cyclopropyl-2-(2-methylcyclopropyl))-4,6- <SEP> 287 <SEP> 174.3
 <tb> pyrimidinediamine
 <tb> 143 <SEP> A-1,2 <SEP> pure <SEP> trans <SEP> N4-cyclohexyl-N6-cyclopropyl-2-(2-methylcyclopropyl) <SEP> -4,6- <SEP> 287 <SEP> 65.25
 <tb> pyrimidinediamine
 <tb>

<Desc/Clms Page number 54>

EMI54.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP> NAME <SEP> MH+ <SEP> (M+#) <SEP> DSC <SEP> C <SEP> (mp) <SEP> alphaD
 <tb> 144 <SEP> B-1,2 <SEP> pure <SEP> trans <SEP> N4-cyclohexyl-N6-cyclopropyl-2-(2-methylcyclopropyl) <SEP> -4,6- <SEP> 287 <SEP> -54.4
 <tb> pyrimidinediamine
 <tb> 145 <SEP> 1 <SEP> maleate <SEP> mixt <SEP> cis <SEP> & <SEP> N4,2-dicyclopropyl-5-methyl-N6-(4-methylcyclohexyl)-4,6- <SEP> 301 <SEP> 166.0
 <tb> trans <SEP> pyrimidinediamine
 <tb> 146 <SEP> A <SEP> pure <SEP> cis <SEP> or <SEP> N4,2-dicyclopropyl-5-methyl-N6-(4-methylcyclohexyl)-4,6- <SEP> 301
 <tb> trans <SEP> pyrimidinediamine
 <tb> 147 <SEP> achiral <SEP> 1-[2-cyclopropyl-6-(cyclopropylamino)-5-methylpyrimidin-4- <SEP> 301
 <tb> yl]azepan-2-one
 <tb> 148 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-6-{3,4-dihydro-2(1H)-

isoquinolinyl)-5- <SEP> 321 <SEP> 196.0
 <tb> methyl-4-pyrimidinamine
 <tb> 149 <SEP> achiral <SEP> N,2-dicyclopropyl-6-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)-5- <SEP> 331
 <SEP> 111.0
 <tb> methyl-4-pyrimidinamine
 <tb> 150 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N4,2-dicyclopropyl-N6-(2,2-diphenylethyl)-
 5-methyl-4,6- <SEP> 385 <SEP> 157.4
 <tb> pyrimidinediamine
 <tb> 151 <SEP> 1 <SEP> maleate <SEP> 1,5 <SEP> mixt <SEP> N,2-dicyclopropyl-5-methyl-6-
 (1,3,3-trimethyl-6- <SEP> 341
 <tb> azabicyclo[3.2.1]oct-6-yl)-4-pyrimidinamine
 <tb> 152 <SEP> 1 <SEP> maleate <SEP> A-4a,8a <SEP> rac <SEP> trans <SEP> N,2-dicyclopropyl-
 5-methyl-6-octahydro-2[1H]-isoquinolinyl-4- <SEP> 327
 <tb> pyrimidinamine
 <tb> 153 <SEP> 1 <SEP> HCl <SEP> achiral <SEP> 6-(8-azaspiro[4.5]dec-8-yl)-N,2-dicyclopropyl-5-
 methyl-4- <SEP> 327
 <tb> pyrimidinamine
 <tb> 154 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 6-(1-azepanyl)-2-cyclopentyl-N-cyclopropyl-
 5-methyl-4- <SEP> 315
 <tb> pyrimidinamine
 <tb>

<Desc/Clms Page number 55>

EMI55.1

<tb> Salt/solvate <SEP> Configuration <SEP> data <SEP> Free <SEP> base <SEP> IUPAC <SEP>
 NAME <SEP> MH+ <SEP> (M+#) <SEP> DSC <SEP> C <SEP> (mp) <SEP> alphaD
 <tb> 155 <SEP> achiral <SEP> 4-azepan-1-yl-2-cyclopropyl-5,6,7,8-tetrahydro-pyrido[2,3- <SEP> 273
 <tb> d]pyrimidine
 <tb> 156 <SEP> achiral <SEP> 4-azepan-1-yl-2-cyclopropyl-6,7,8,9-tetrahydro-pyrimido[4,5- <SEP>
 287
 <tb> b]azepine
 <tb> 157 <SEP> achiral <SEP> 4-azepan-1-yl-2-cyclopropyl-6,7-dihydro-pyrrolo[2,3d]pyrimidine
 <tb> 172 <SEP> 1 <SEP> fumarate <SEP> 1R,2R & <SEP> rac <SEP> trans <SEP> 6-(1-azepanyl)-2-
 cyclopropyl-5-methyl-N-(2- <SEP> 301 <SEP> 138.0
 <tb> 1S,2S <SEP> methylcyclopropyl)-4-pyrimidinamine
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 (cyclopropylamino)-2-(2-methylcyclopropyl)-4- <SEP> 303 <SEP> 127.76
 <tb> pyrimidinyl]-4-piperidinyl}methanol
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 <tb> fumarate <SEP> methylcyclopropyl)-4-pyrimidinamine
 <tb> 175 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> N,2-dicyclopropyl-5-methyl-6-(1-
 piperidinyl)-4-pyrimidinamine <SEP> 273 <SEP> 110.1
 <tb> 176 <SEP> 1 <SEP> maleate <SEP> achiral <SEP> 6-(3-azabicyclo[3.2.2]non-3-yl)-N,2-
 dicyclopropyl-5-methyl-4- <SEP> 313
 <tb> pyrimidinamine
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 methyl-1-piperidinyl)-4- <SEP> 287 <SEP> 186.3

<tb> pyrimidinamine
 <tb> 178 <SEP> achiral <SEP> N4,2-dicyclopropyl- <SEP> N6-(4-fluorobenzyl)-5-methyl-4,6- <SEP> 313
 <tb> pyrimidinediamine
 <tb> 179 <SEP> achiral <SEP> N4,2-dicyclopropyl-5-methyl-N6-(2-methylbenzyl)-4,6- <SEP> 309
 <tb> pyrimidinediamine
 <tb>

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EMI56.1

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 <tb> pyrimidinamine
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 <tb> 4-yl]azepane
 <tb> 183 <SEP> achiral <SEP> 1-[6-azepan-1-yl-2-cyclopropyl-5-methylpyrimidin-4- <SEP> 312
 <tb> yl)azetidine-3-carbonitrile
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 <tb> 4-yl]azepane
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 <tb> yl)azetidin-3-ol
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EMI57.1

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 pyrimidin-4- <SEP> 287 <SEP> 159.1
 <tb> yl]azepane
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 <SEP> 77.5
 <tb> 193 <SEP> 1 <SEP> H2O <SEP> achiral <SEP> 1-(6-azepan-1-yl-2-cyclopropyl-5-
 methylpyrimidin-4- <SEP> 319
 <tb> yl)azetidin-3-one
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 305
 <tb> yl]azepane
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 <SEP> 291 <SEP> 129.9
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 5- <SEP> 317
 <tb> methylpyrimidin-4-yl]azepane
 <tb>

compound 97 was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/isohexane/diethylamine 5/95/0.1 (v/v), 30 C) to give compound 99 (first eluted) and compound 100 (second eluted).

Compound 65 was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/isohexane/diethylamine 5/95/0.1, 30 C) to give compound 67 (second eluted) and compound 68 (first eluted).

5 Compound 142 was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/isohexane/diethylamine 3/97/0.1, 30 C) to give compound 143 (first eluted) and compound 144 (second eluted).

Compound 101 was resolved into its enantiomers by chromatography on a chiral support (Chiralpak AD Daicel, isopropanol/hexane mixture 4/96, 30 C) to give compound 104 (first eluted) and compound 105 (second eluted).

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EXAMPLE 8: affinity for human muscarinic receptors.

Chinese Hamster Ovarian cells(CHO) expressing the human recombinantml, m2,m3, m4 andm5 receptors were cultured in Ham's F12 media supplemented with 100IU/ml of penicillin,100ug/n-il of streptomycin, 400jD. g/ml ofgeneticin and 5 % of fetal bovine serum. Cell cultures were maintained in a humidified incubator at 37 C and 5%CO2.

Confluent CHO cells expressing humanml, m2, m3, m4 and m5 muscarinic receptors were harvested

and resuspended in phosphate buffered saline without calcium and magnesium. The cell suspension was centrifuged at 1500 x g for 3 min (4 C). The cell pellet was homogenized in a 15mM Tris-HCl (pH 7.5) buffer containing 2 mM MgCl₂, 0.3 mM EDTA and 1 mM EGTA. The crude membrane fraction was collected by two consecutive centrifugation steps at 40,000 x g for 25 min (4 C). The final pellet was resuspended, at a protein concentration ranging from 2 to 6 mg/ml, in a 7.5 mM Tris-HCl (pH 7.5) buffer containing 12.5 mM MgCl₂, 0.3 mM EDTA, 1 mM EGTA and 250 mM sucrose and stored in liquid nitrogen.

Binding assays were performed according to procedure described in: Buckley N. J. , Bonner T. I. , Buckley C.M., Brann M. R. , Mol. Pharmacol. (1989), 35,469-476, but with slight modifications.

Briefly, 25 to 50 mg of membrane proteins were incubated at room temperature in 1 ml of a 50 mM Tris-HCl (pH 7.4) buffer containing 2 mM of MgCl₂, 0.1 nM of [3H]- NMS (N-methylscopolamine, 85 Ci/mmol, from Apbiotech, UK) and increasing concentrations of test compound dissolved in DMSO (1 % final concentration). Non specific binding was measured in the presence of 1 μ M atropine. After 60 (m2) or 120 (m3) min. incubation, assays were stopped by rapid vacuum filtration of the samples through glass fiber filters (Filtermat A, Wallac, Belgium) presoaked in 0.3 % polyethyleneimine for at least 2 h. Samples were further rinsed with 8 ml of ice-cold 50 mM Tris-HCl (pH 7.4) buffer. Radioactivity trapped onto the filter was counted in a Betaplate counter (Wallac). Competition binding curves were analyzed by non-linear regression with XLfit software (IDBS, UK).

EXAMPLE 9: PDE IV enzymatic activity.

Enzyme source:

Cytosolic fraction from U937 cells pre-stimulated for 4 h at 37 C with a mixture of rolipram 30 μ M and salbutamol 1 μ M (Torphy T. J., Zhou H, L. , Cieslinski L.B., J. Pharmacol. Exp. Ther. (1992), 263 (3), 1195-1205).

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SPA Phosphodiesterase assay (Amersham. Pharmacia Biotech ; Belgium) :

Assays were performed in 100 μ l of 50 mM Tris HCl buffer (pH 7.4) containing 5 mM : MgCl₂, 2 mM EGTA, 20 nM of [3H]-cAMP (40-60 Ci/mmol), the cytosolic fraction of 50,000 U937 cells and the appropriate concentration of test compound (usually 10 μ M) dissolved in DMSO (final assay concentration not exceeding 1%). After 30 min incubation at room temperature, 0.5 mg of SPA yttrium silicate beads are added to each sample. Radioactivity bound to the beads (5'-AMP) is determined by liquid scintillation. Non PDE IV activity and/or non specific binding of the labeled substrate to the SPA beads is defined as the residual radioactivity remaining in the presence of rolipram 32 μ M (non PDE IV activity represents about 40 % of total activity). PDE IV activity is determined by subtracting the non PDE IV activity from the total activity.

Compounds according to the invention showed pIC₅₀ values ranging from 6.5 to 10 for the m3 receptor, and showed pIC₅₀ values ranging from 5.7 to 8 for PDE IV.

Dual high affinities were especially shown by compounds 55, 56, 57, 59, 60, 61, 62, 63, 64, 65, 66, 67, 72, 77, 78, 79, 80, 86, 87, 94, 95, 98, 106, 112, 115, 118, 119, 132, 144, 145, 154, 155, 156, 175, 176, 177, 180, 184, 185, 186, 187, 189, 191, 192 and 194.

EXAMPLE 10 : in vitro inhibition of carbachol-induced contraction of guinea-pig trachea.

The method was developed according to the procedure described in Leff P., Dougall I.G., Harper D., Br. J. Pharmacol. (1993), 110, 239-244. tracheal rings were prepared from male Dunkin-Hartley guinea pig. Tissues were mounted in 20ml organ baths containing modified Krebs' solution in the presence of 3×10^{-6} M indomethacin, 3×10^{-4} M hexamethonium and 10^{-6} M propranolol. The bathing solution was maintained at 37 °C and gassed with 95 % O₂-5 % CO₂. Tissues were allowed to equilibrate for a period of 60 min under a resting tension of 1 g. Isometric contractions were measured by force-displacement transducers coupled to an IOX computer system capable of controlling automatic data acquisition and bath washout by automatic fluid circulation through electrovalves at defined times. Drugs were manually or robotically injected into the bath according to the stability of the measured signal.

At the end of the 60 min period of stabilisation, the tracheas were contracted twice with 10^{-6} M carbachol at 30 min intervals. Two cumulative concentration-response curves were successively constructed in the absence or presence of the test

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compound (incubation time: 1 hour). Results were obtained from at least 3 or 4 individual experiments. Control tissues were treated with the solvent.

Antagonistic potency of the test compound was estimated by the calculation of pD'₂ and/or pA₂ values according to the methods described by Van Rossum (Van Rossum J. M., Hurkmans J. A. T.M., Wolters C. J. J., Arch. Int. Pharmacodyn. Ther.

(1963), 143, 299-330) or Arunlakshana & Schild (Arunlakshana O., Schild H.O., Br. J.

Pharmacol. (1959), 14, 48-58).

Preferred compounds according to the invention show pA₂ values typically ranging from 5.5 to 8.